

# EXHIBIT A



US007423055B2

(12) **United States Patent**  
**Ciufolini et al.**

(10) **Patent No.:** **US 7,423,055 B2**  
(45) **Date of Patent:** **\*Sep. 9, 2008**

(54) **2-(3-AMINOARYL)AMINO-4-ARYL-THIAZOLES  
FOR THE TREATMENT OF DISEASES**

(75) Inventors: **Marco Ciufolini**, Lyons (FR); **Camille  
Wermuth**, Strasbourg (FR); **Bruno  
Gielthen**, Illkirch (FR); **Alain Moussy**,  
Paris (FR)

(73) Assignee: **AB Science**, Paris (FR)

(\*) Notice: Subject to any disclaimer, the term of this  
patent is extended or adjusted under 35  
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-  
claimer.

(21) Appl. No.: **10/632,101**

(22) Filed: **Aug. 1, 2003**

(65) **Prior Publication Data**

US 2004/0110810 A1 Jun. 10, 2004

**Related U.S. Application Data**

(60) Provisional application No. 60/400,064, filed on Aug.  
2, 2002.

(51) **Int. Cl.**

**A61K 31/44** (2006.01)

**C07D 417/04** (2006.01)

**C07D 417/14** (2006.01)

(52) **U.S. Cl.** ..... **514/342**; 514/370; 546/270.4;  
548/194; 544/364

(58) **Field of Classification Search** ..... 548/190,  
548/194; 546/270.4; 514/342, 370  
See application file for complete search history.

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

3,192,225 A 6/1965 Spivack et al.

3,201,409 A \* 8/1965 Dexter et al. .... 548/193  
3,467,666 A \* 9/1969 Dexter et al. .... 548/193  
5,521,184 A 5/1996 Zimmermann  
6,291,514 B1 \* 9/2001 Illig et al. .... 514/447  
2001/0044545 A1 \* 11/2001 Dhanoa et al. .... 548/190  
2003/0158199 A1 \* 8/2003 Stieber et al. .... 514/242

#### FOREIGN PATENT DOCUMENTS

WO WO-96/01825 A1 \* 1/1996  
WO WO 99/03854 A 1/1999  
WO WO 00/33842 A 5/2000  
WO WO 00/75120 A 12/2000  
WO WO 01/64200 A 9/2001  
WO WO 01/64674 A 9/2001  
WO WO 02/080925 A 10/2002  
WO WO 03/062215 A 7/2003

#### OTHER PUBLICATIONS

Golub et al., Science, vol. 286, Oct. 15, 1999, pp. 531-537.\*  
Schantl et al., Synthetic Communications (1998), 28(8), pp. 1451-  
1462.\*

\* cited by examiner

*Primary Examiner*—Laura L. Stockton

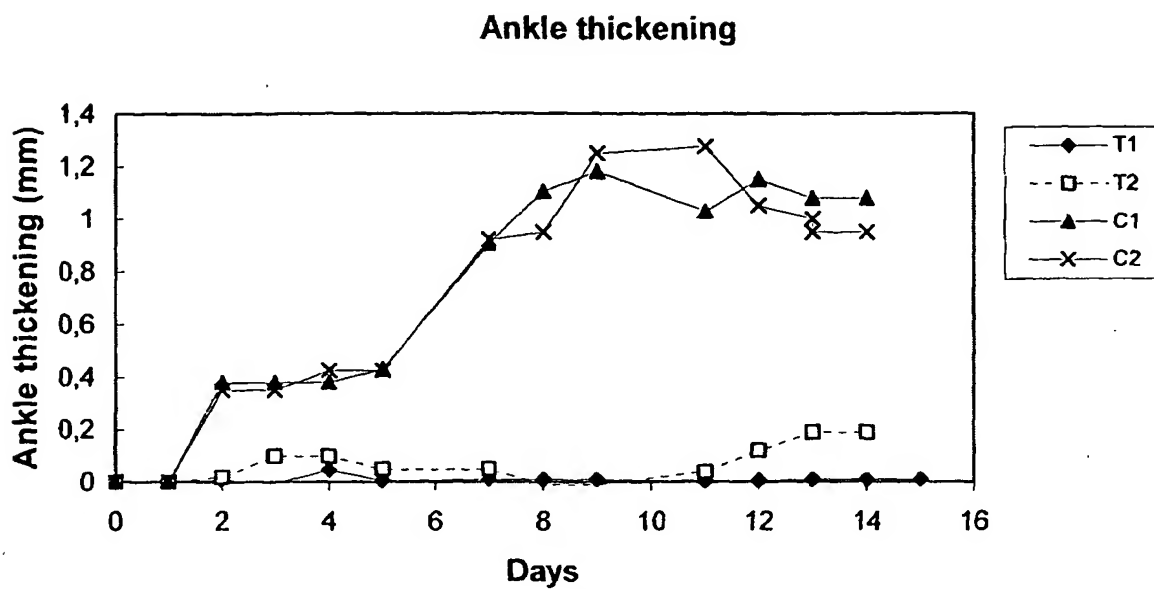
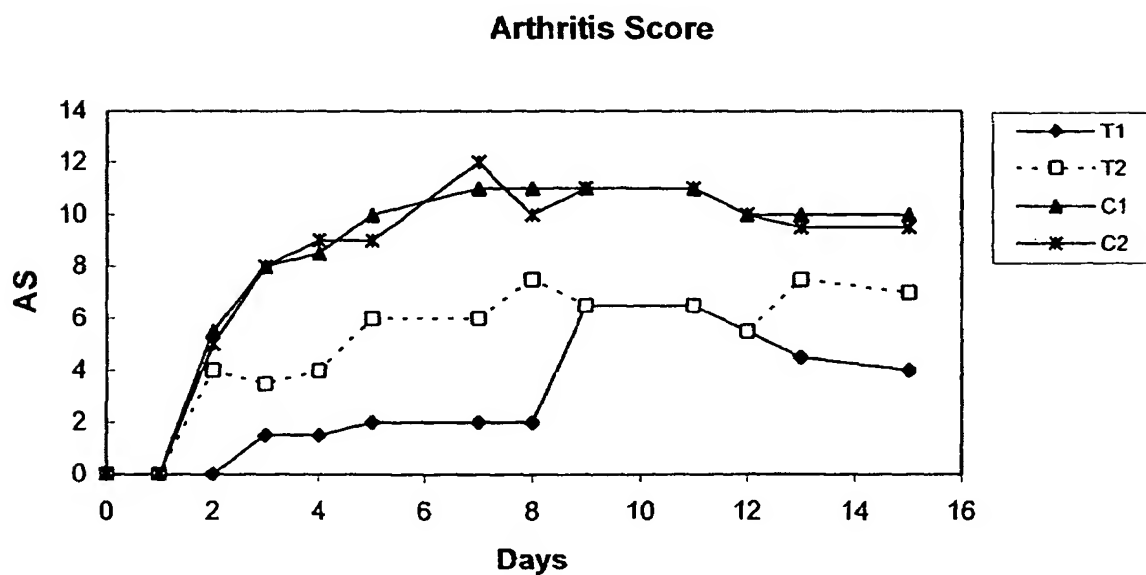
(74) *Attorney, Agent, or Firm*—Foley & Lardner

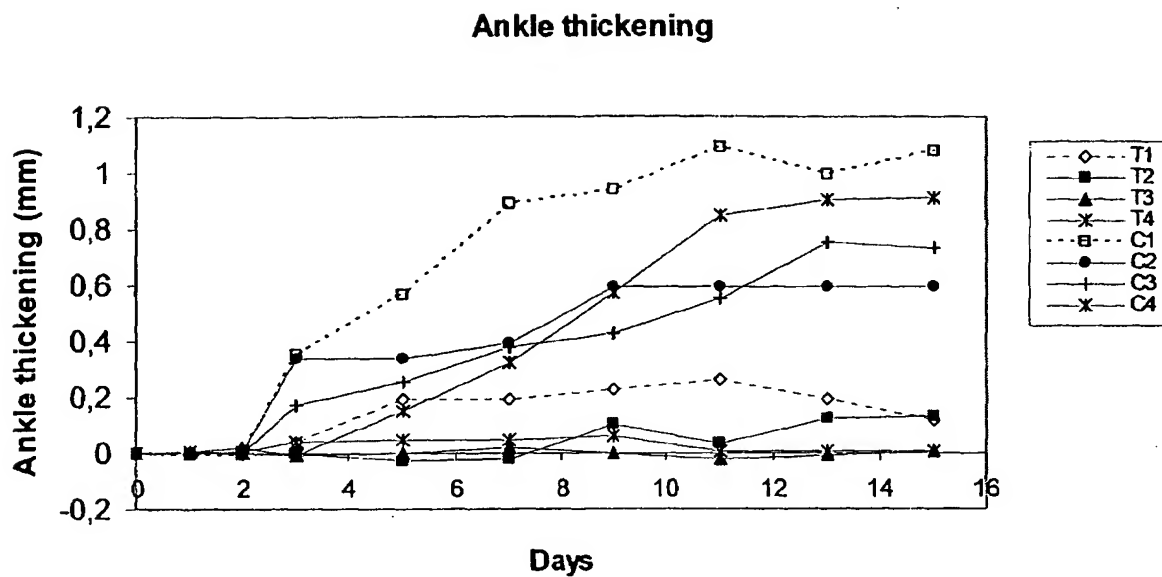
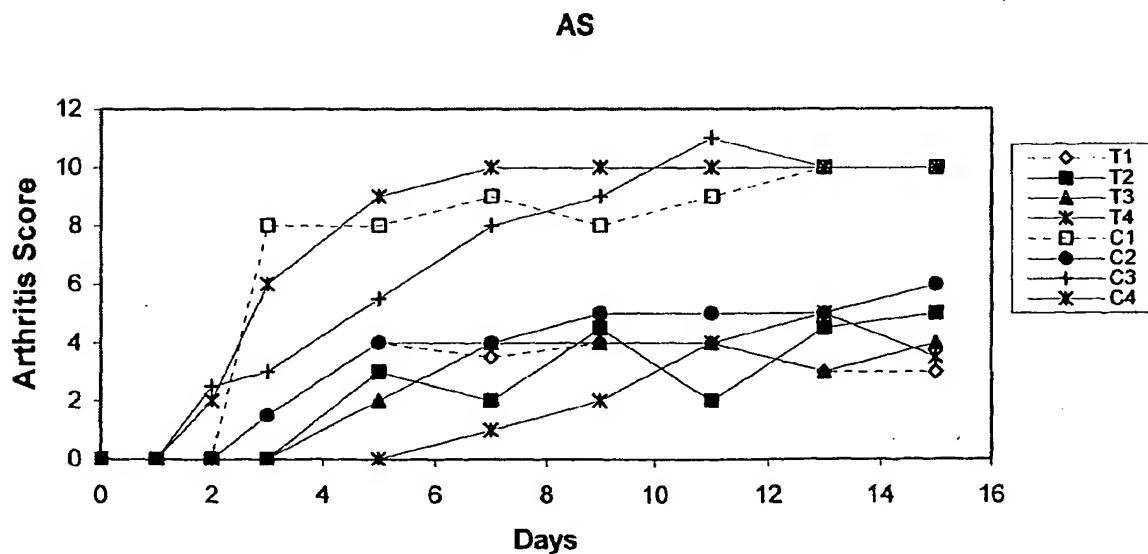
(57) **ABSTRACT**

The present invention relates to novel compounds selected  
from 2-(3-aminoaryl)amino-4-aryl-thiazoles that selectively  
modulate, regulate, and/or inhibit signal transduction medi-  
ated by certain native and/or mutant tyrosine kinases impli-  
cated in a variety of human and animal diseases such as cell  
proliferative, metabolic, allergic, and degenerative disorders.  
More particularly, these compounds are potent and selective  
c-kit inhibitors.

**30 Claims, 2 Drawing Sheets**



**FIGURE 1****FIGURE 2**

**FIGURE 3****FIGURE 4**

## 2-(3-AMINOARYL)AMINO-4-ARYL-THIAZOLES FOR THE TREATMENT OF DISEASES

### BACKGROUND OF THE INVENTION

The present invention relates to novel compounds selected from 2-(3-aminoaryl)amino-4-aryl-thiazoles that selectively modulate, regulate, and/or inhibit signal transduction mediated by certain native and/or mutant tyrosine kinases implicated in a variety of human and animal diseases such as cell proliferative, metabolic, allergic, and degenerative disorders. More particularly, these compounds are potent and selective c-kit inhibitors.

Tyrosine kinases are receptor type or non-receptor type proteins, which transfer the terminal phosphate of ATP to tyrosine residues of proteins thereby activating or inactivating signal transduction pathways. These proteins are known to be involved in many cellular mechanisms, which in case of disruption, lead to disorders such as abnormal cell proliferation and migration as well as inflammation.

As of today, there are about 58 known receptor tyrosine kinases. Other tyrosine kinases are the well-known VEGF receptors (Kim et al., Nature 362, pp. 841-844, 1993), PDGF receptors, c-kit and the FLK family. These receptors can transmit signals to other tyrosine kinases including Src, Raf, Frk, Btk, Csk, Abl, Fes/Fps, Fak, Jak, Ack. etc.

Among tyrosine kinase receptors, c-kit is of special interest. Indeed, c-kit is a key receptor activating mast cells, which have proved to be directly or indirectly implicated in numerous pathologies for which the Applicant filed WO 03/004007, WO 03/004006, WO 03/003006, WO 03/003004, WO 03/002114, WO 03/002109, WO 03/002108, WO 03/002107, WO 03/002106, WO 03/002105, WO 03/039550, WO 03/035050, WO 03/035049, U.S. 60/359,652 and U.S. 60/359,651.

It was found that mast cells present in tissues of patients are implicated in or contribute to the genesis of diseases such as autoimmune diseases (rheumatoid arthritis, inflammatory bowel diseases (IBD)) allergic diseases, tumor angiogenesis, inflammatory diseases, and interstitial cystitis. In these diseases, it has been shown that mast cells participate in the destruction of tissues by releasing a cocktail of different proteases and mediators such as histamine, neutral proteases, lipid-derived mediators (prostaglandins, thromboxanes and leucotrienes), and various cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, TNF- $\alpha$ , GM-CSF, MIP-1a, MIP-1b, MIP-2 and IFN- $\gamma$ ).

The c-kit receptor also can be constitutively activated by mutations leading to abnormal cell proliferation and development of diseases such as mastocytosis and various cancers.

For this reason, it has been proposed to target c-kit to deplete the mast cells responsible for these disorders.

The main objective underlying the present invention is therefore to find potent and selective compounds capable of inhibiting wild type and/or mutated c-kit.

Many different compounds have been described as tyrosine kinase inhibitors, for example, bis monocyclic, bicyclic or heterocyclic aryl compounds (WO 92/20642), vinylene-azaindole derivatives (WO 94/14808) and 1-cyclopropyl-4-pyridyl-quinolones (U.S. Pat. No. 5,330,992), styryl compounds (U.S. Pat. No. 5,217,999), styryl-substituted pyridyl compounds (U.S. Pat. No. 5,302,606), selenindoles and selenides (WO 94/03427), tricyclic polyhydroxylic compounds (WO 92/21660) and benzylphosphonic acid compounds (WO 91/15495), pyrimidine derivatives (U.S. Pat. No. 5,521,184 and WO 99/03854), indolinone derivatives and pyrrole-substituted indolinones (U.S. Pat. No.

5,792,783, EP 934 931, U.S. Pat. No. 5,834,504, U.S. Pat. No. 5,883,116, U.S. Pat. No. 5,883,113, U.S. Pat. No. 5,886,020, WO 96/40116 and WO 00/38519), as well as bis monocyclic, bicyclic aryl and heteroaryl compounds (EP 584 222, U.S. Pat. No. 5,656,643 and WO 92/20642), quinazoline derivatives (EP 602 851, EP 520 722, U.S. Pat. No. 3,772,295 and U.S. Pat. No. 4,343,940) and aryl and heteroaryl quinazoline (U.S. Pat. No. 5,721,237, U.S. Pat. No. 5,714,493, U.S. Pat. No. 5,710,158 and WO 95/15758).

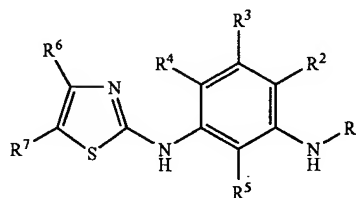
However, none of these compounds have been described as potent and selective inhibitors of c-kit or of the c-kit pathway.

In connection with the present invention, we have found that compounds corresponding to the 2-(3-aminoaryl)amino-4-aryl-thiazoles are potent and selective inhibitors of c-kit or c-kit pathway. These compounds are good candidates for treating diseases such as autoimmune diseases, inflammatory diseases, cancer and mastocytosis.

### BRIEF SUMMARY OF THE INVENTION

Therefore, the present invention relates to compounds belonging to the 2-(3-amino)arylamino-4-aryl-thiazoles. These compounds are capable of selectively inhibiting signal transduction involving the tyrosine phosphokinase c-kit and mutant forms thereof. In a first embodiment, the invention is aimed at compounds of formula I, which may represent either free base forms of the substances or pharmaceutically acceptable salts thereof:

FORMULA I



and wherein R<sup>1</sup> is:

- a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;
- an aryl or heteroaryl group optionally substituted by an alkyl or aryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;
- a —CO—NH—R, —CO—R, —CO—OR or a —CO—NRR' group, wherein R and R' are independently chosen from H or an aryl, heteroaryl, alkyl and cycloalkyl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

R<sup>2</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>3</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>4</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>5</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

3

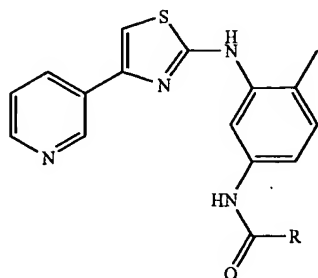
R<sup>6</sup> is one of the following:

- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy,
- iv) H, a halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>—R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; and R<sup>7</sup> is one of the following:
  - (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
  - (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
  - (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.
  - iv) H, a halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>—R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

#### DETAILED DESCRIPTION OF INVENTION

The present invention provides compounds belonging to the 2-3-(amino)arylamino-4-aryl-thiazoles, such as those described above with reference to Formula I. These compounds are capable of selectively inhibiting signal transduction involving the tyrosine phosphokinase c-kit and mutant forms thereof.

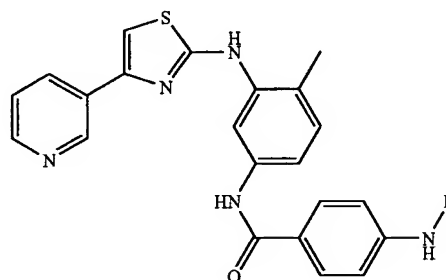
In another preferred embodiment, when R<sup>1</sup> has the meaning depicted in c) above, the invention is directed to compounds of the following formula:



4

wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality.

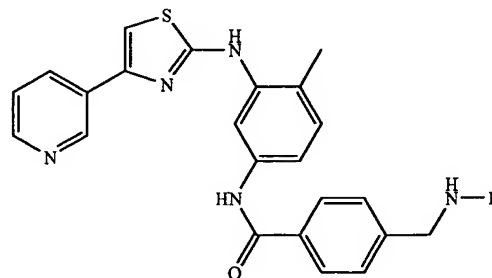
Among the particular compounds in which R1 has the meaning as depicted in c) above, the invention is directed to amide-aniline compounds of the following formula:



wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality;

a —SO<sub>2</sub>—R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality; or a —CO—R or a —CO—NRR' group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

Among the particular compounds in which R1 has the meaning as depicted in c) above, the invention is directed to amide-benzylamine compounds of the following formula:



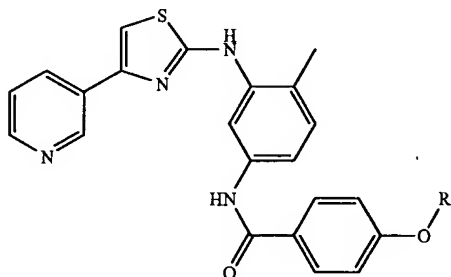
wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing

5

from 1 to 10 carbon atoms optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or an alkyl, cycloalkyl, aryl or heteroaryl group substituted by a alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a —SO<sub>2</sub>—R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a —CO—R or a —CO—NRR' group, wherein R and R' are independently chosen from H or an aryl heteroaryl, alkyl and cycloalkyl group optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality.

Among the particular compounds in which R1 has the meaning as depicted in c) above, the invention is directed to amide-phenol compounds of the following formula:



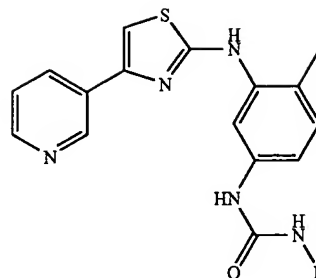
wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

a cycloalkyl, aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality; or an alkyl, cycloalkyl, aryl or heteroaryl group substituted by a alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality;

a —SO<sub>2</sub>—R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality; or a —CO—R or a —CO—NRR' group, wherein R and R' are independently chosen from H or an aryl, heteroaryl, alkyl and cycloalkyl group optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality.

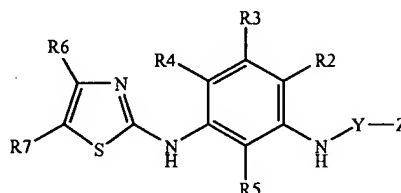
Among the particular compounds in which R1 has the meaning as depicted in c) above, the invention is directed to urea compounds of the following formula:

6



wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

Among the particular compounds in which R1 has the meaning as depicted in a) and b) above, the invention is directed to N-Aminoalkyl-N'-thiazol-2-yl-benzene-1,3-diamine compounds of the following formula:



wherein Y is a linear or branched alkyl group containing from 1 to 10 carbon atoms;

wherein Z represents an aryl or heteroaryl group, optionally substituted at one or more ring position with any permutation of the following groups:

a halogen such as F, Cl, Br, I;

a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

an O—R, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom,

an NHCOOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or

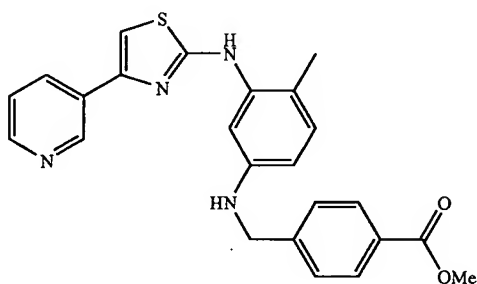
60 (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

65 (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.
- iv) H, a halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>—R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; and R<sup>7</sup> is one of the following:
- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
  - (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
  - (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.
- iv) H, an halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>—R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

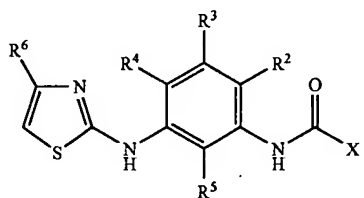
An example of preferred compounds of the above formula is depicted below:

001: 4-[[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylamino]-methyl]-benzoic acid methyl ester



Among the compounds of formula I, the invention is particularly embodied by the compounds of the following formula II:

FORMULA II



wherein X is R or NRR' and wherein R and R' are independently chosen from H, an aryl, a heteroaryl, an alkyl, or a cycloalkyl group optionally substituted with at least one heteroatom, such as for example a halogen chosen from F, I, Cl and Br and optionally bearing a pendant basic nitrogen functionality; or an aryl, a heteroaryl, an alkyl or a cycloalkyl group substituted with an aryl, a heteroaryl, an alkyl or a cycloalkyl group optionally substituted with at least one heteroatom, such as for example a halogen chosen from F, I, Cl and Br and optionally bearing a pendant basic nitrogen functionality,

R<sup>2</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>3</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>4</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>5</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

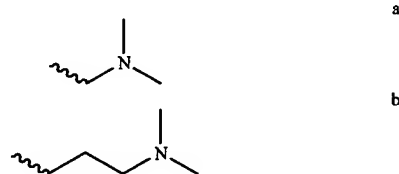
R<sup>6</sup> is one of the following:

- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.

- iv) H, a halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>—R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

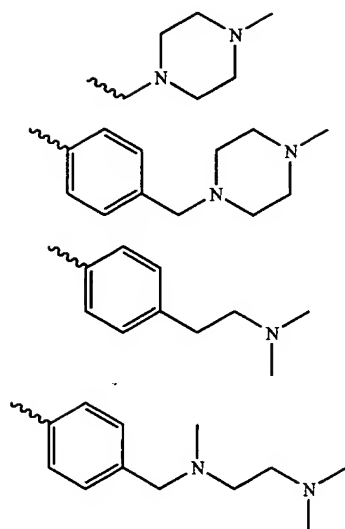
In another alternative, substituent R<sup>6</sup>, which in the formula II is connected to position 4 of the thiazole ring, may instead occupy position 5 of the thiazole ring.

Among the preferred compounds corresponding formula II, the invention is directed to compounds in which X is a substituted alkyl, aryl or heteroaryl group bearing a pendant basic nitrogen functionality represented for example by the structures a to f shown below, wherein the wavy line corresponds to the point of attachment to core structure of formula II:



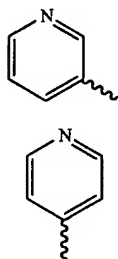
11

-continued



Among group a to f, X (see formula II) is preferentially group d.

Furthermore, among the preferred compounds of formula I or II, the invention concerns the compounds in which R<sup>2</sup> and R<sup>3</sup> are hydrogen. Preferentially, R<sup>4</sup> is a methyl group and R<sup>5</sup> is H. In addition, R<sup>6</sup> is preferentially a 3-pyridyl group (cf. structure g below), or a 4-pyridyl group (cf. structure h below). The wavy line in structure g and h correspond to the point of attachment to the core structure of formula I or II.



Thus, the invention contemplates:

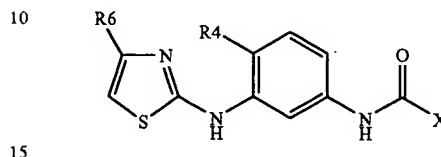
- 1—A compound of formula II as depicted above, wherein X is group d and R<sup>6</sup> is a 3-pyridyl group.
- 2—A compound of formula II as depicted above, wherein X is group d and R<sup>4</sup> is a methyl group.
- 3—A compound of formula I or II as depicted above, wherein R<sup>1</sup> is group d and R<sup>2</sup> is H.
- 4—A compound of formula I or II as depicted above, wherein R<sup>1</sup> is group d and R<sup>3</sup> is H.
- 5—A compound of formula I or II as depicted above, wherein R<sup>1</sup> is group d and R<sup>2</sup> and/or R<sup>3</sup> and/or R<sup>5</sup> is H.
- 6—A compound of formula I or II as depicted above, wherein R<sup>6</sup> is a 3-pyridyl group and R<sup>3</sup> is a methyl group.
- 7—A compound of formula I or II as depicted above, wherein R<sup>6</sup> is a 3-pyridyl group and R<sup>2</sup> is H.
- 8—A compound of formula I or II as depicted above, wherein R<sup>2</sup> and/or R<sup>3</sup> and/or R<sup>5</sup> is H and R<sup>4</sup> is a methyl group.

12

9—A compound of formula I or II as depicted above wherein R<sup>2</sup> and/or R<sup>3</sup> and/or R<sup>5</sup> is H, R<sup>4</sup> is a methyl group and R<sup>6</sup> is a 3-pyridyl group.

Among the compounds of formula II, the invention is particularly embodied by the compounds wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup> are hydrogen, corresponding to the following formula II-1:

FORMULA II-1



wherein X is R or NRR' and wherein R and R' are independently chosen from H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a —SO<sub>2</sub>-R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a —CO—R or a —CO—NRR' group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

R<sup>4</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>6</sup> is one of the following:

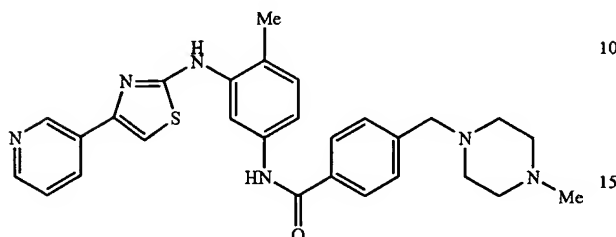
- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.
- iv) H, a halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

In another alternative, substituent R<sub>6</sub>, which in the formula II is connected to position 4 of the thiazole ring, may instead occupy position 5 of the thiazole ring.

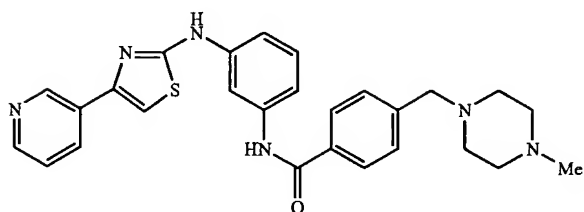


**13**  
EXAMPLES

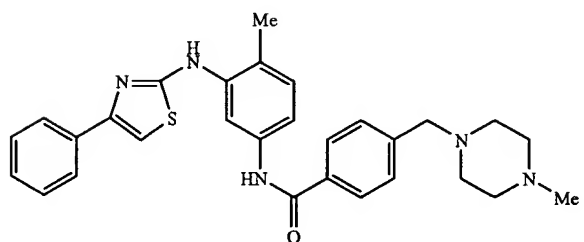
002: 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



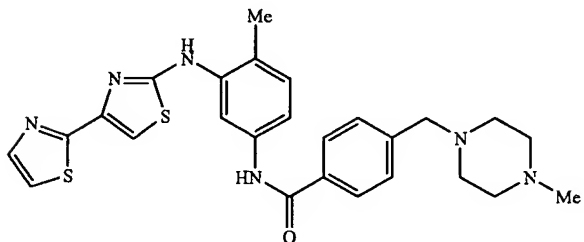
003: 4-(4-Methyl-piperazin-1-ylmethyl)-N-[3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



004: N-[4-Methyl-3-(4-phenyl-thiazol-2-ylamino)-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide

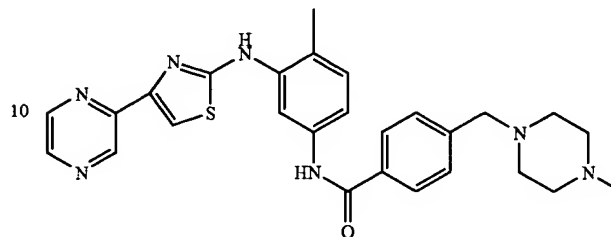


005: N-[3-([2,4']Bithiazolyl-2'-ylamino)-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide

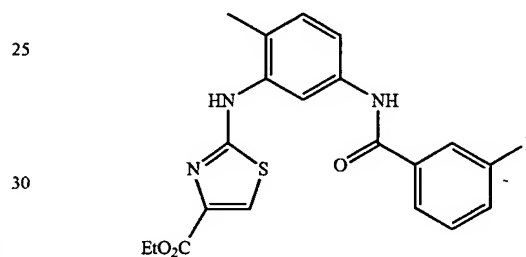


**14**

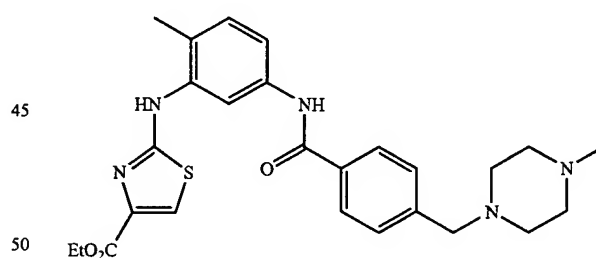
006: 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyrazin-2-yl-thiazol-2-ylamino)-phenyl]-benzamide



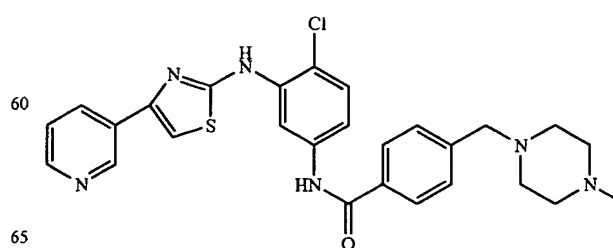
007: 2-[5-(3-Iodo-benzoylamino)-2-methyl-phenylamino]-thiazole-4-carboxylic acid ethyl ester



008: 2-{2-Methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-benzoylamino]-phenylamino}-thiazole-4-carboxylic acid ethyl ester

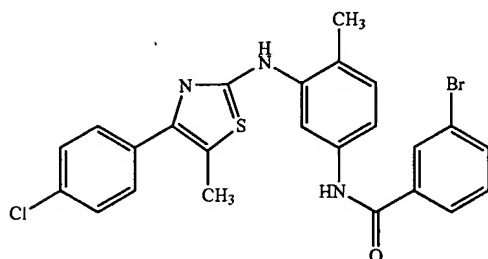


027: N-(4-chloro-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl)-4-(4-methyl-piperazin-1-ylmethyl)benzamide

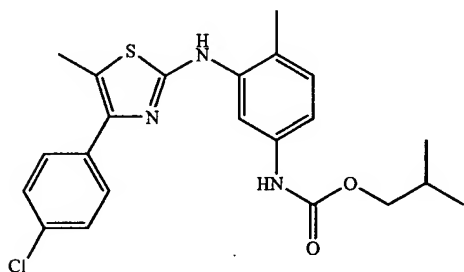


15

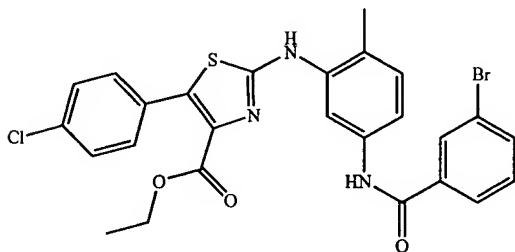
128: 3-Bromo-N-{3-[4-(4-chloro-phenyl)-5-methyl-thiazol-2-ylamino]-4-methyl-phenyl}-benzamide



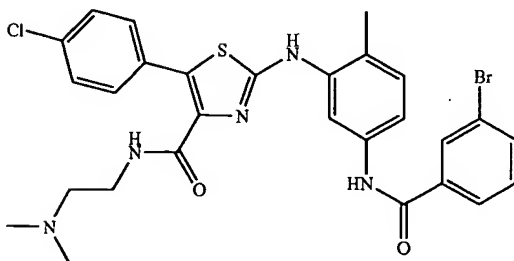
129: {3-[4-(4-Chloro-phenyl)-5-methyl-thiazol-2-ylamino]-4-methyl-phenyl}-carbamic acid isobutyl ester



130: 2-[5-(3-Bromo-benzoylamino)-2-methyl-phenylamino]-5-(4-chloro-phenyl)-thiazole-4-carboxylic acid ethyl ester

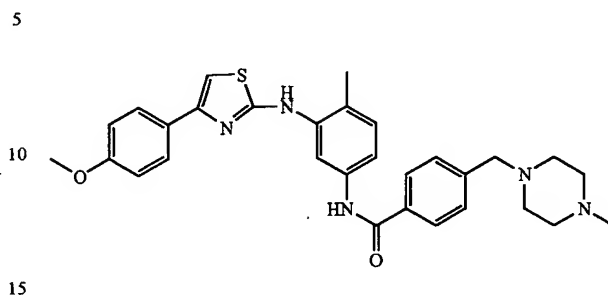


131: 2-[5-(3-Bromo-benzoylamino)-2-methyl-phenylamino]-5-(4-chloro-phenyl)-thiazole-4-carboxylic acid (2-dimethylamino-ethyl)-amide

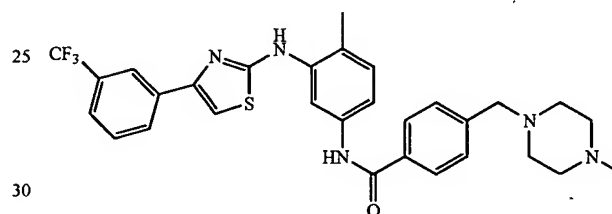


16

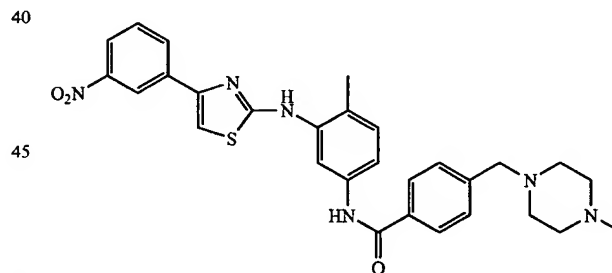
110: N-{3-[4-(4-Methoxy-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



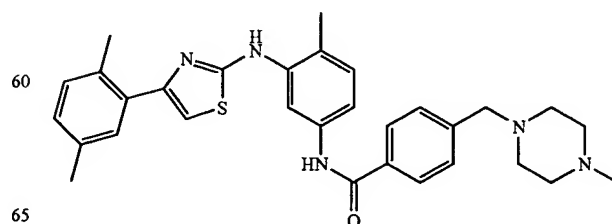
116: 4-(4-Methyl-piperazin-1-ylmethyl)-N-{4-methyl-3-[4-(3-trifluoromethyl-phenyl)-thiazol-2-ylamino]-phenyl}-benzamide



117: N-{4-Methyl-3-[4-(3-nitro-phenyl)-thiazol-2-ylamino]-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide

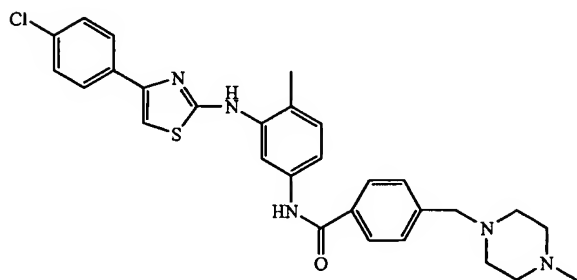


124: N-{3-[4-(2,5-Dimethyl-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



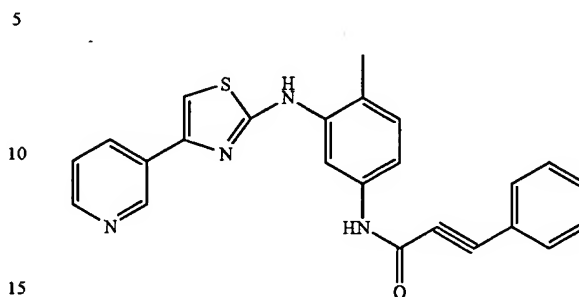
17

108: N-{3-[4-(4-Chloro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide

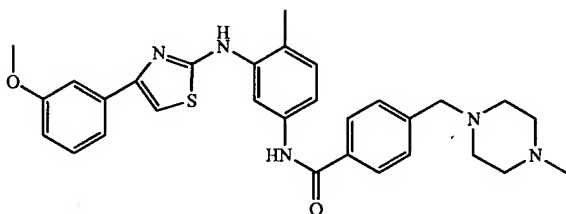


18

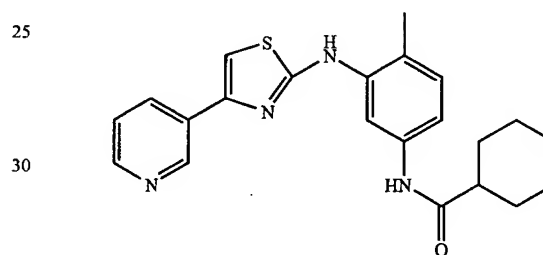
091: 3-Phenyl-propynoic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide



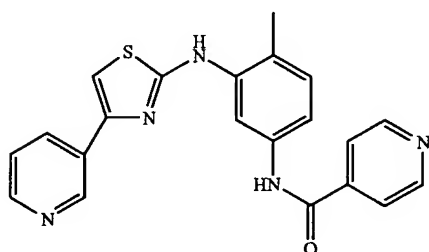
113: N-{3-[4-(3-Methoxy-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



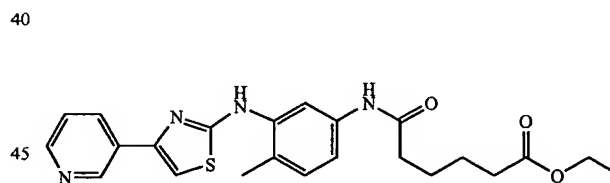
092: Cyclohexanecarboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide



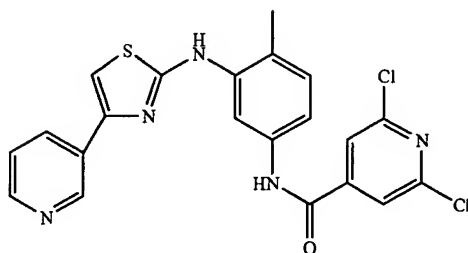
063: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-isonicotinamide



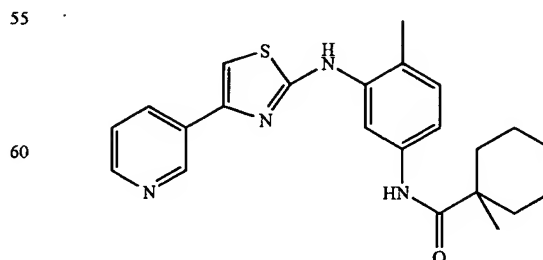
093: 5-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-pentanoic acid ethyl ester



064: 2,6-Dichloro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-isonicotinamide

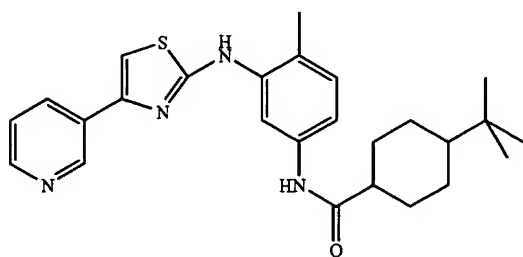


094: 1-Methyl-cyclohexanecarboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide



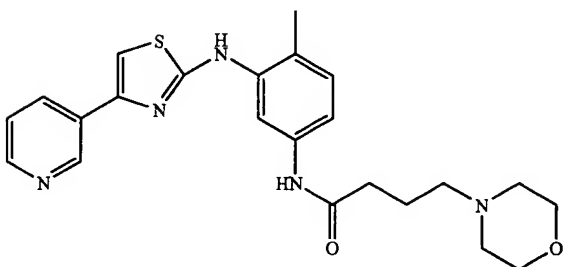
19

095: 4-tert-Butyl-cyclohexanecarboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide



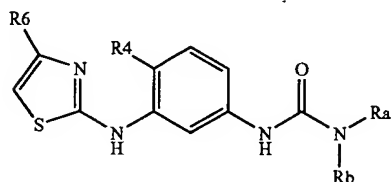
mixture of isomers  
cis/trans

096: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-morpholin-4-yl-butyramide



beige powder mp: 116-120° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>)  
δ=1.80-2.00 (m, 2H); 2.29 (s, 3H); 2.30-2.45 (m, 6H); 3.55-3.65 (m, 6H); 7.15-7.25 (m, 2H); 7.46-7.50 (m, 2H); 7.52 (s, 1H); 8.35 (d, J=6.2 Hz, 1H); 8.55 (dd, J=1.5 Hz, J=4.7 Hz, 2H); 9.22 (s, 1H); 9.45 (s, 1H); 9.93 (s, 1H)

Among the compounds of formula II, the invention is particularly embodied by the compounds wherein X is a urea group, a —CO—NRR' group, corresponding to the [3-(thiazol-2-ylamino)-phenyl]-urea family and the following formula II-2:



FORMULA II-2

wherein Ra, Rb are independently chosen from H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

20

a —SO<sub>2</sub>-R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a —CO—R or a —CO—NRR' group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, or bearing a pendant basic nitrogen functionality.

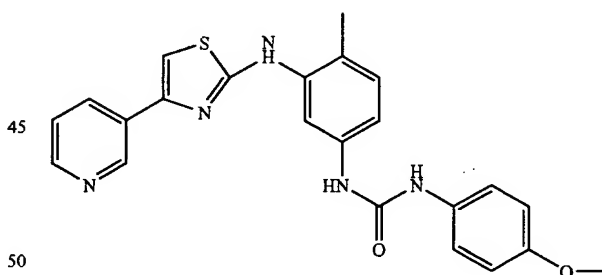
R<sup>4</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>6</sup> is one of the following:

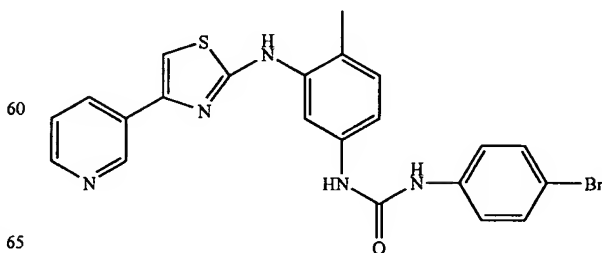
- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.
- iv) H, a halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

## EXAMPLES

009: 1-(4-Methoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

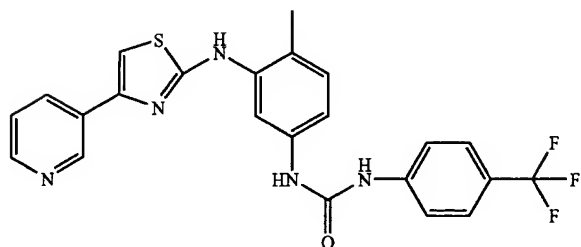


010: 1-(4-Bromo-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



21

011: 1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(4-trifluoromethyl-phenyl)-urea



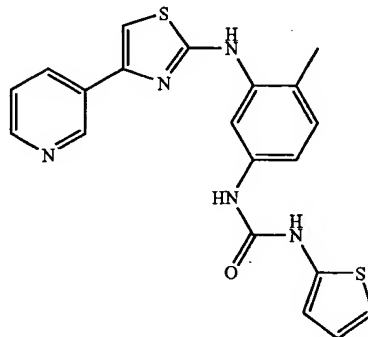
5

10

15

22

015: 1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(thiophen-2-yl)-urea

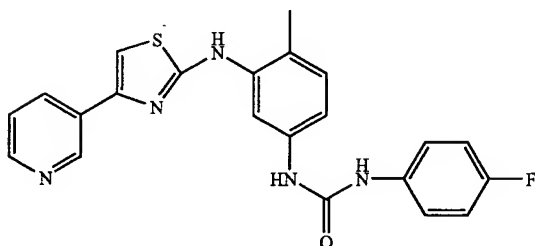


20

25

30

012: 1-(4-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

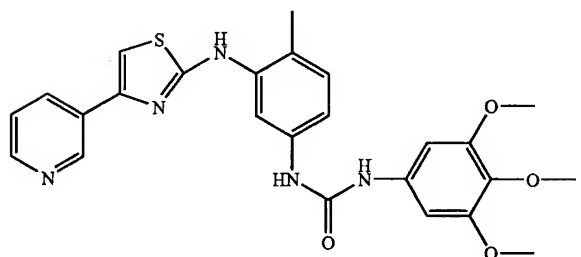


35

40

45

013: 1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(3,4,5-trimethoxy-phenyl)-urea



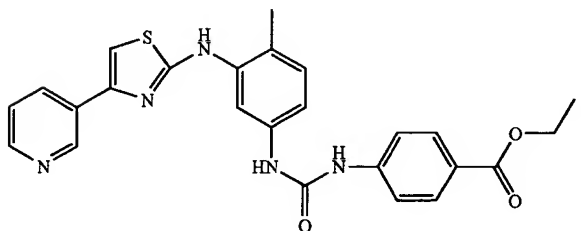
50

55

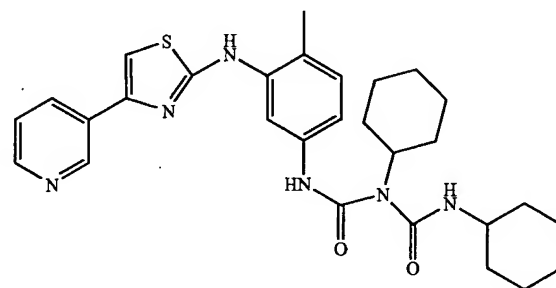
60

65

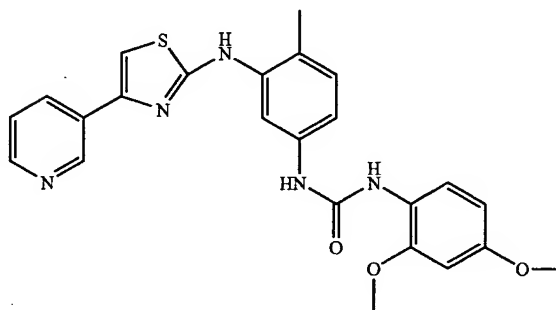
014: 4-{3-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-ureido}-benzoic acid ethyl ester



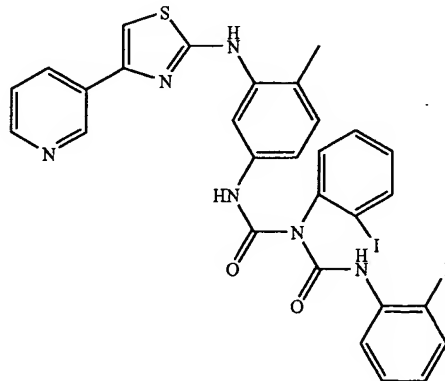
016: 1-Cyclohexyl-1-(N-Cyclohexyl-formamide)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



017: 1-(2,4-Dimethoxy-phenyl)-3-[4-methyl-2-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

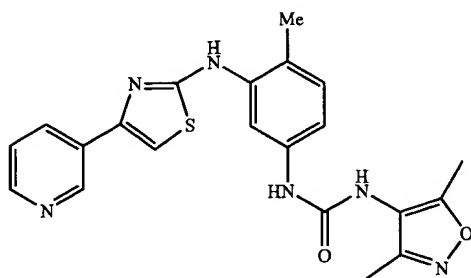


018: 1-(2-Iodo-phenyl)-1-(N-(2-Iodo-phenyl)-formamide)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

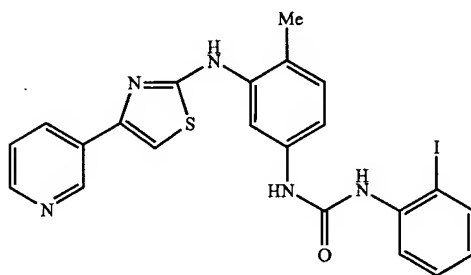


23

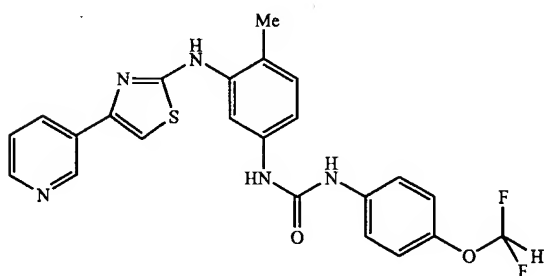
019: 1-(3,5-Dimethyl-isoxazol-4-yl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



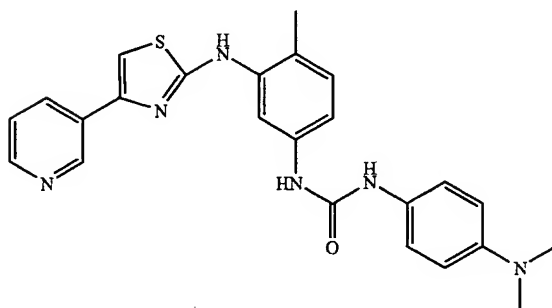
020: 1-(2-Iodo-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



021: 1-(4-Difluoromethoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

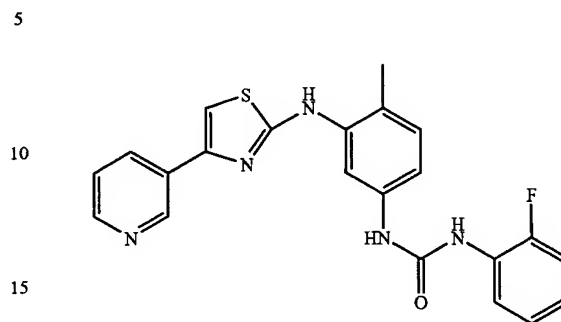


022: 1-(4-Dimethylamino-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



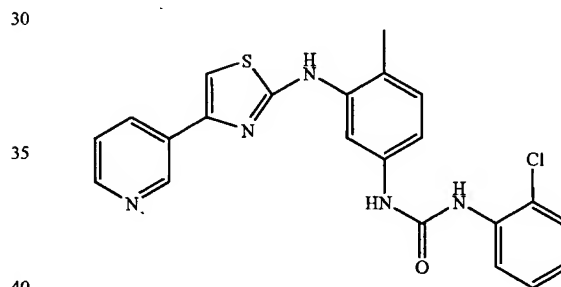
24

023: 1-(2-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

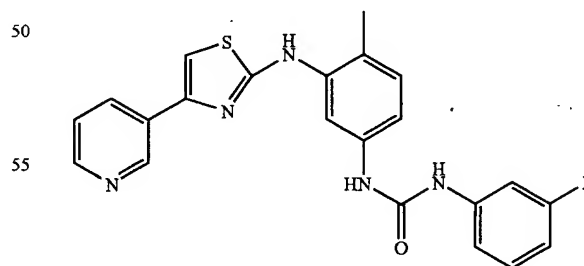


light brown powder mp: 203-206° C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ=2.24 (s, 3H); 6.98-7.00 (m, 2H); 7.10-7.23 (m, 3H); 7.40 (m, 1H); 7.48 (s, 1H); 8.25 (m, 1H); 8.37 (d, J=7.8 Hz, 1H); 8.51 (m, 3H); 9.03 (s, 1H); 9.19 (s, 1H); 9.39 (s, 1H)

024: 1-(2-Chloro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



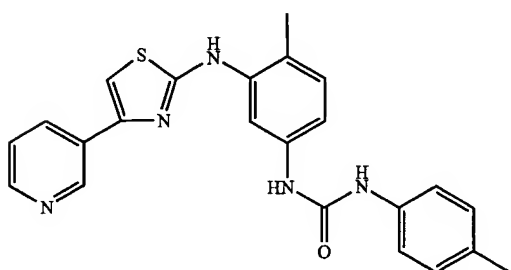
025: 1-(3-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



white powder mp: 210-215° C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.24 (s, 3H); 6.79 (t, J=6.3 Hz, 1H); 6.99 (m, 1H); 7.09-7.14 (m, 2H); 7.30 (m, 1H); 7.41 (t, J=4.7 Hz, 1H); 7.48 (s, 1H); 7.56 (d, J=1.2 Hz, 1H); 8.39 (d, J=8.0 Hz, 1H); 8.49-8.52 (m, 2H); 8.71 (s, 1H); 8.87 (s, 1H); 9.18 (s, 1H); 9.38 (s, 1H)

25

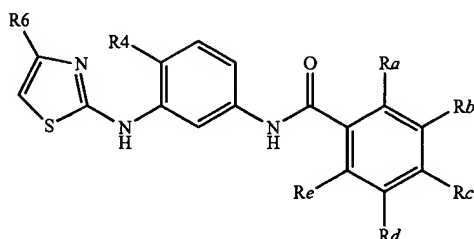
026: 1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-p-tolyl-urea



white powder mp: 238-240° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.29 (s, 3H); 2.31 (s, 3H); 7.05 (d, J=6.2 Hz, 1H); 7.10-1.16 (m, 3H); 7.42-7.49 (m, 3H); 7.53 (s, 1H); 8.35-8.62 (m, 5H); 9.22 (d, J=1.6 Hz, 1H); 9.43 (s, 1H)

Among the compounds of formula II, the invention is particularly embodied by the compounds wherein X is a substituted Aryl group, corresponding to the N-[3-(Thiazol-2-ylamino)-phenyl]-amide family and the following formula II-3:

FORMULA II-3



wherein Ra, Rb, Rc, Rd, Re are independently chosen from H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a —SO<sub>2</sub>-R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a —CO—R or a —CO—NRR' group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, and or bearing a pendant basic nitrogen functionality;

Ra, Rb, Rc, Rd, Re may also be a halogen such as I, Cl, Br and F

a NRR' group where R and R' are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a

26

cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

an OR group where R is H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; a —SO<sub>2</sub>-R' group wherein R' is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a NRaCORb group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a NRaCONRbRc group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a COOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

a CONRaRb, where Ra and Rb are a hydrogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at

27

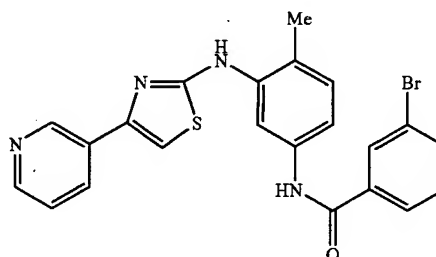
- least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;
- an NHCOOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;
- an OSO<sub>2</sub>R, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;
- an NRAOSO<sub>2</sub>Rb, where Ra and Rb are a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; Ra can also be a hydrogen; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;
- a CN group
- a trifluoromethyl group
- R<sup>4</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;
- R<sup>6</sup> is one of the following:
- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
  - (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
  - (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

28

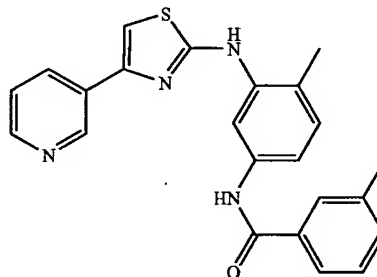
- iv) H, a halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

## EXAMPLES

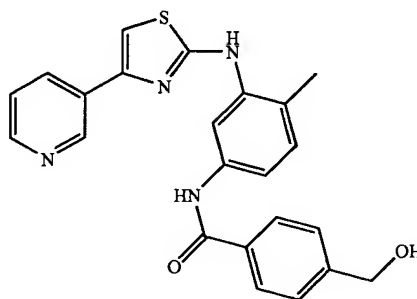
- 028: 3-Bromo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



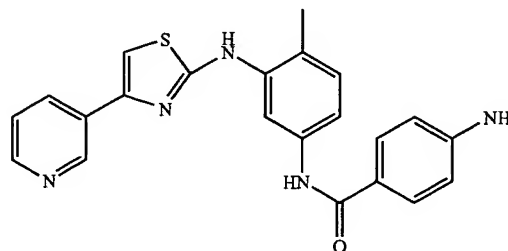
- 029: 3-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



- 030: 4-Hydroxymethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



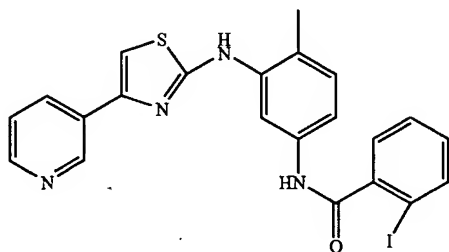
- 031: 4-Amino-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



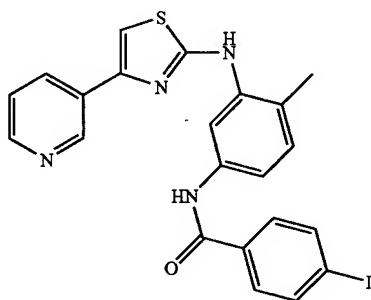


29

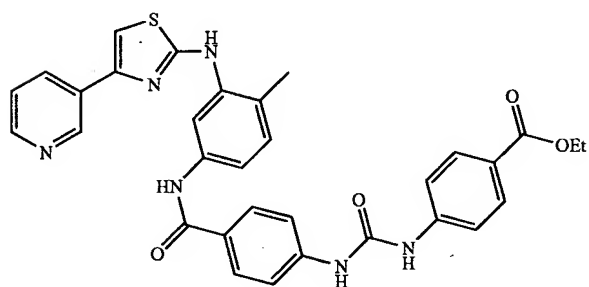
032: 2-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



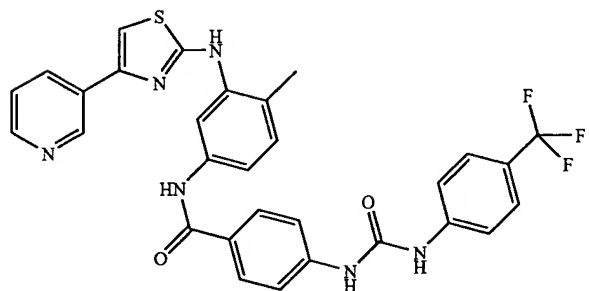
033: 4-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



034: 4-(3-{4-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl}-ureido)-benzoic acid ethyl ester

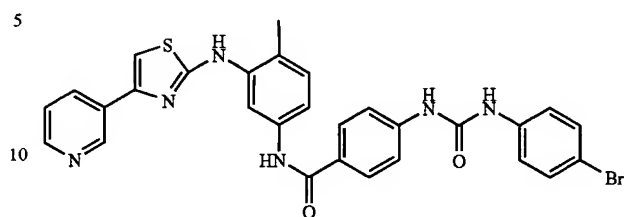


035: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide

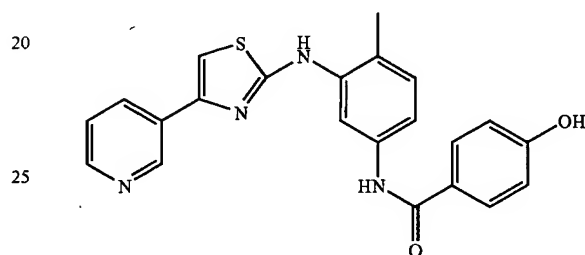


30

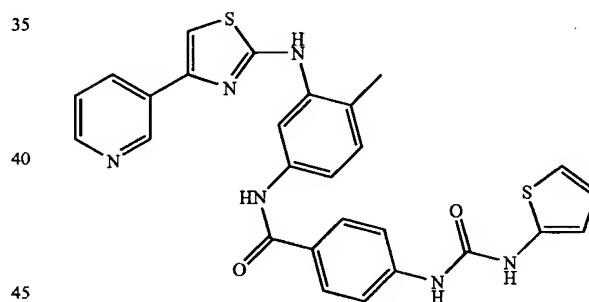
036: 4-[3-(4-Bromo-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



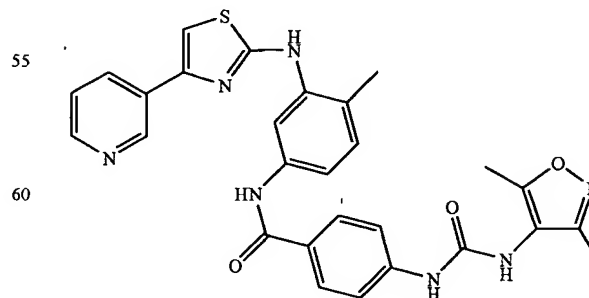
037: 4-Hydroxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



038: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-(3-thiophen-2-yl-ureido)-benzamide

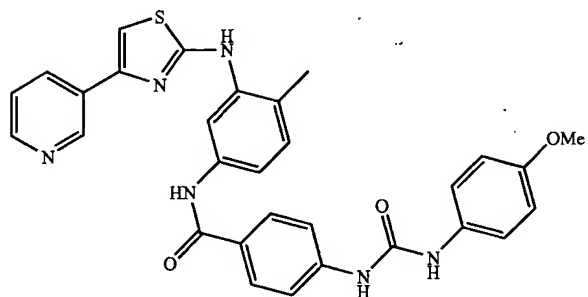


039: 4-[3-(3,5-Dimethyl-isoxazol-4-yl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

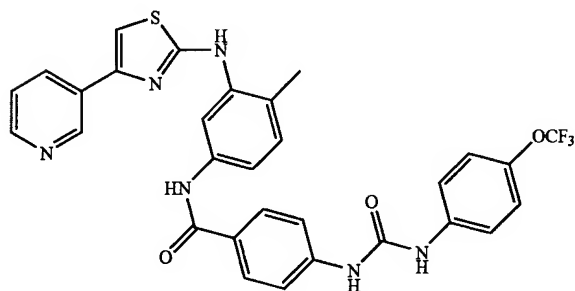


31

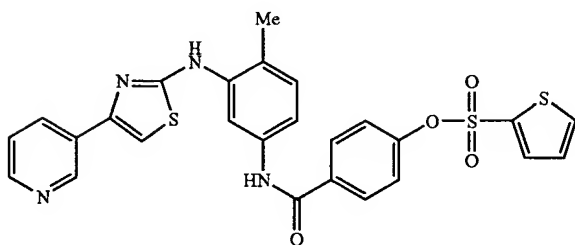
040: 4-[3-(4-Methoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



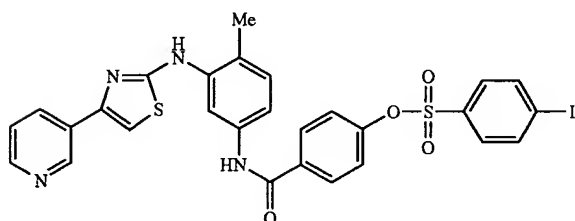
041: 4-[3-(4-Difluoromethoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



042: Thiophene-2-sulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester

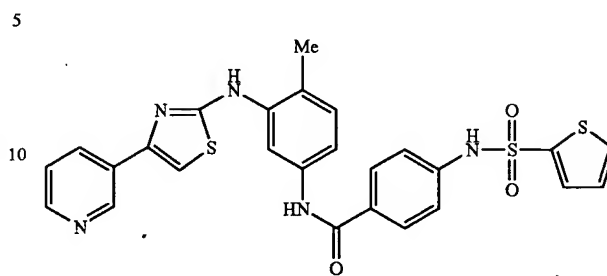


043: 4-Iodo-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester



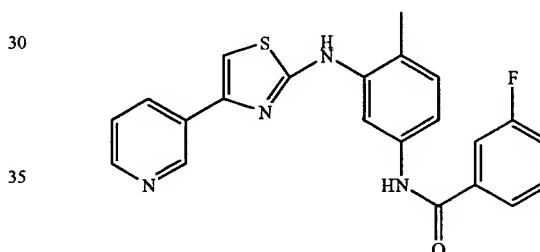
32

044: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]4-(thiophene-2-sulfonylamino)-benzamide



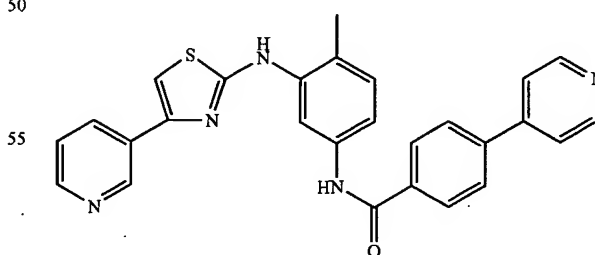
brown powder mp: 230-233° C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ=2.29 (s, 3H); 7.15-7.18 (m, 2H); 7.22-7.32 (m, 3H); 7.48 (m, 2H); 7.67 (dd, J=1.3 Hz, J=3.7 Hz, 1H); 7.90-7.96 (m, 3H); 8.38-8.42 (m, 1H); 8.51 (m, 1H); 8.57 (d, J=1.9 Hz, 1H); 9.17 (d, J=1.7 Hz, 1H); 9.44 (s, 1H); 10.12 (s, 1H); 10.82 (s, 1H)

045: 3-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



off-white foam mp: 184-186° C. <sup>1</sup>H NMR (CD<sub>3</sub>OD-d<sub>4</sub>): δ=2.23 (s, 3H); 7.12-7.14 (m, 2H); 7.20-7.23 (m, 2H); 7.30 (m, 1H); 7.43 (m, 1H); 7.50 (m, 1H); 7.66 (d, J=1.0 Hz, 1H); 8.23 (m, 1H); 8.33 (m, 1H); 8.38 (s, 1H); 8.98 (s, 1H)

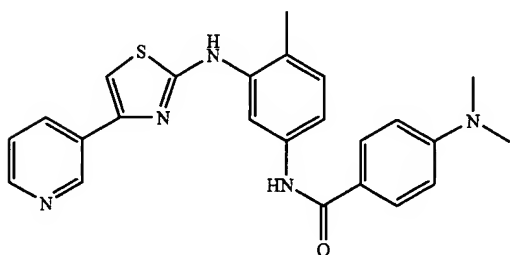
046: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-pyridin-4-yl-benzamide



yellow powder mp: 254-256° C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.34 (s, 3H); 7.28 (d, J=8.0 Hz, 1H); 7.45-7.49 (m, 2H); 7.54 (s, 1H); 7.78 (t, J=7.6 Hz, 1H); 7.89-7.91 (m, 2H); 8.10 (t, J=7.8 Hz, 2H); 8.37-8.42 (m, 2H); 8.55 (d, J=4.7 Hz, 1H); 8.73-8.77 (m, 3H); 9.24 (s, 1H); 9.52 (s, 1H); 10.43 (s, 1H)

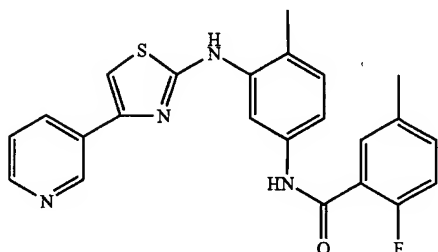
33

047: 4-Dimethylamino-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



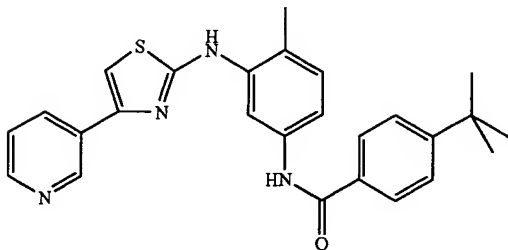
beige powder mp: 147-150° C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.25 (s, 3H); 2.99 (s, 6H); 6.76 (d, J=8.9 Hz, 2H); 7.16 (d, J=8.3 Hz, 1H); 7.35 (d, J=2.0 Hz, 1H); 7.44-7.47 (m, 2H); 7.86-7.89 (m, 2H); 8.34-8.36 (m, 1H); 8.48-8.50 (m, 1H); 8.56-8.57 (m, 1H); 9.16 (s, 1H); 9.44 (s, 1H); 9.85 (s, 1H)

048: 2-Fluoro-5-methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



brown orange powder mp: 103-106° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.26 (s, 3H); 2.35 (s, 3H); 7.17-7.47 (m, 7H); 8.29 (dd, J=1.6 Hz, J=7.9 Hz, 1H); 8.47 (d, J=3.5 Hz, 1H); 8.57 (s, 1H); 9.15 (d, J=2.0 Hz, 1H); 9.44 (s, 1H); 10.33 (s, 1H)

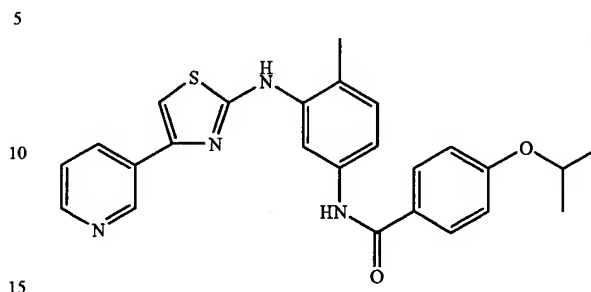
049: 4-tert-Butyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



brown powder mp: 145-150° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=1.32 (s, 9H); 2.04 (s, 3H); 7.18 (d, J=8.4 Hz, 1H); 7.35-7.44 (m, 2H); 7.46 (s, 1H); 7.55 (d, J=8.5 Hz, 1H); 7.90 (d, J=8.5 Hz, 1H); 8.32 (d, J=7.9 Hz, 1H); 8.47 (dd, J=1.5 Hz, J=4.7 Hz, 1H); 8.60 (d, J=2.0 Hz, 1H); 9.15 (d, J=1.7 Hz, 1H); 9.43 (s, 1H); 10.15 (s, 1H)

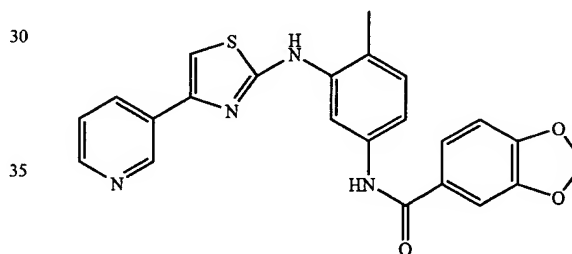
34

050: 4-Isopropoxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



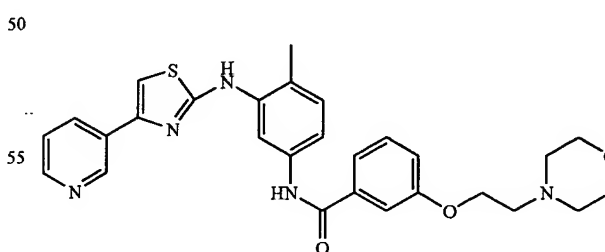
brown powder mp: 154-155° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=1.34 (d, J=5.9 Hz, 6H); 4.72 (hept, J=5.9 Hz, 1H); 7.01 (d, J=7.0 Hz, 2H); 7.18 (d, J=8.5 Hz, 1H); 7.35-7.44 (m, 2H); 7.46 (s, 1H); 7.94 (dd, J=2.0 Hz, J=6.7 Hz, 2H); 8.32 (d, J=8.3 Hz, 1H); 8.48 (dd, J=3.3 Hz, J=4.8 Hz, 1H); 8.58 (d, J=2.0 Hz, 1H); 9.15 (d, J=1.8 Hz, 1H); 9.43 (s, 1H); 10.4 (s, 1H)

051: Benzo[1,3]dioxole-5-carboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide



brown orange powder mp: 130-132° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.23 (s, 3H); 6.10 (s, 2H); 7.03 (d, J=8.1 Hz, 1H); 7.15 (d, J=8.3 Hz, 1H); 7.25-7.55 (m, 6H); 8.26 (s, 1H); 8.45 (dd, J=1.5 Hz, J=4.7, 1H); 8.55 (d, J=2.0 Hz, 1H); 9.12 (d, J=1.7 Hz, 1H); 9.40 (s, 1H); 10.01 (s, 1H)

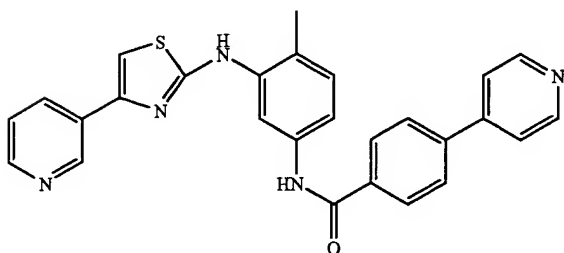
052: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(2-morpholin-4-yl-ethoxy)-benzamide



beige yellow powder mp: 75-80° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.10-2.25 (m, 4H); 2.50-2.60 (m, 2H); 3.19 (s, 3H); 3.41-3.48 (m, 4H); 4.00-4.06 (m, 2H); 7.00-7.11 (m, 2H); 7.22-7.35 (m, 6H); 8.18 (d, J=8.0 Hz, 1H); 8.33 (d, J=0.9 Hz, 1H); 8.49 (d, J=1.7 Hz, 1H); 9.03 (s, 1H); 9.31 (s, 1H); 10.05 (s, 1H)

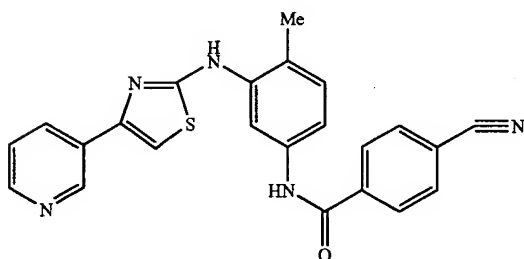
35

053: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-pyridin-4-yl-benzamide

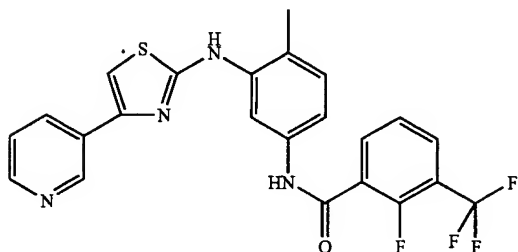


brown powder mp: dec. 250° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.28 (s, 3H); 7.21 (d, J=7.9 Hz, 1H); 7.30-7.50 (m, 3H) 7.81 (d, J=4.7 Hz, 1H); 7.98 (d, J=7.5 Hz, 2H); 8.13 (d, J=7.9 Hz, 2H); 8.32 (d, J=7.7 Hz, 1H); 8.48 (d, J=4.9 Hz, 1H); 8.62-8.69 (m, 3H); 9.16 (s, 1H); 9.45 (s, 1H) 10.34 (s, 1H)

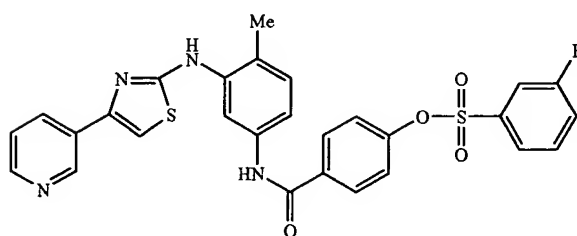
054: 3-Cyano-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



055: 2-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide

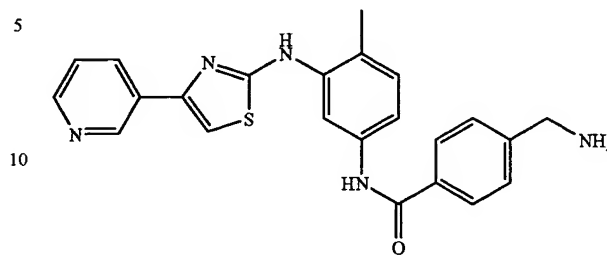


056: 3-Fluoro-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester

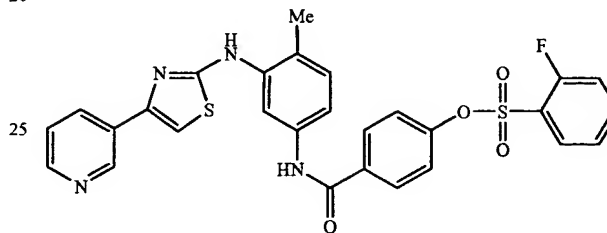


36

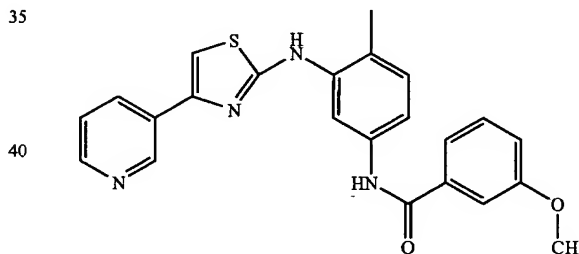
057: 4-Aminomethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



058: 2-Fluoro-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester

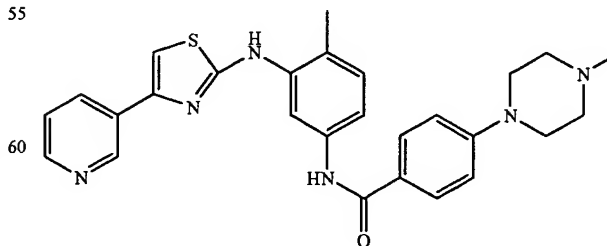


059: 3-Methoxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



white powder mp: 76-79° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.32 (s, 3H); 3.89 (s, 3H); 7.22-7.25 (m, 2H); 7.44-7.58 (m, 4H); 8.28-8.35 (m, 1H); 8.52 (dd, J=1.6 Hz, J=4.7 Hz, 1H); 8.66 (d, J=2.0 Hz, 1H); 9.20 (d, J=1.4 Hz, 1H); 9.50 (s, 1H); 10.25 (s, 1H)

060: 4-(4-Methyl-piperazin-1-yl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-benzamide

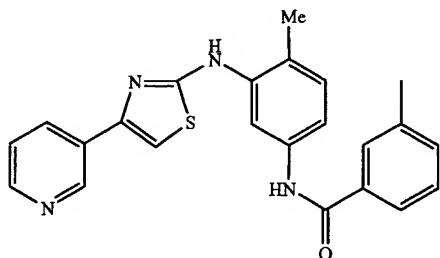


beige brown powder mp: 128-130° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.15 (s, 3H); 2.18 (s, 3H); 2.35-2.41 (m, 4H); 3.18-

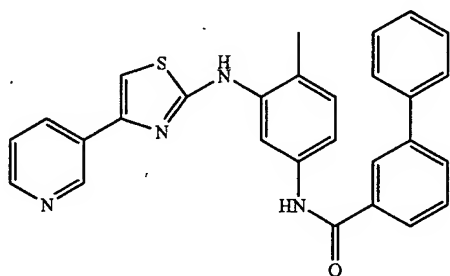
37

3.3.24 (m, 4H); 6.94 (d, J=8.9 Hz, 2H); 7.09 (d, J=8.4 Hz, 1H); 7.28-7.38 (m, 3H); 7.81 (d, J=8.9 Hz, 2H); 8.20-8.25 (m, 1H); 8.40 (dd, J=1.6 Hz, J=4.7, 1H); 8.48 (d, J=1.9 Hz, 1H); 9.07 (d, J=1.5 Hz, 1H); 9.35 (s, 1H); 9.84 (s, 1H)

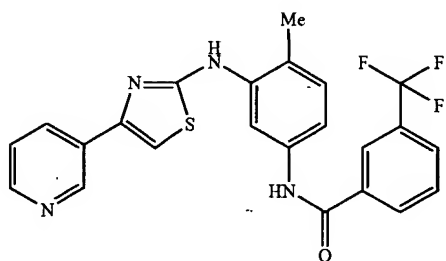
061: 3-Methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



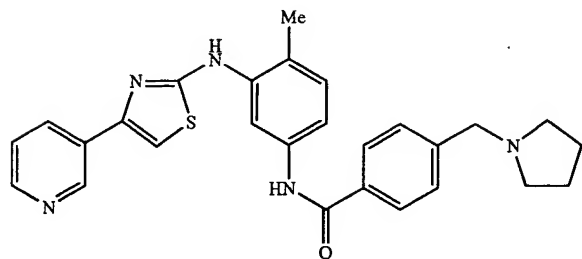
062: Biphenyl-3-carboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide



065: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide

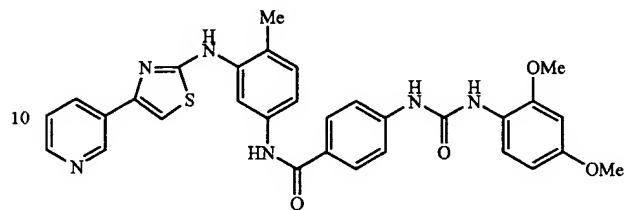


099: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-pyrrolidin-1-ylmethyl-benzamide

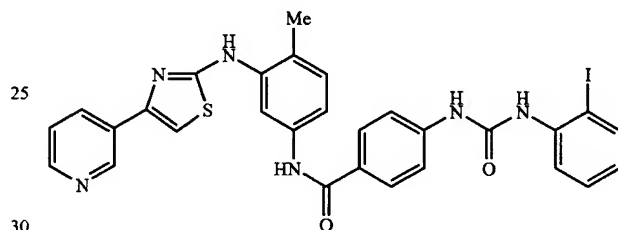


38

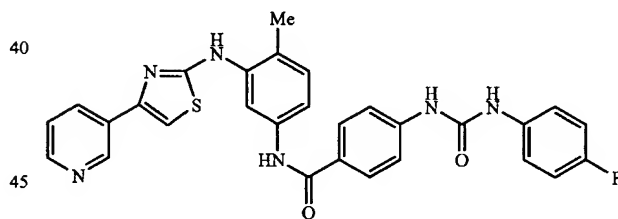
100: 4-[3-(2,4-Dimethoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



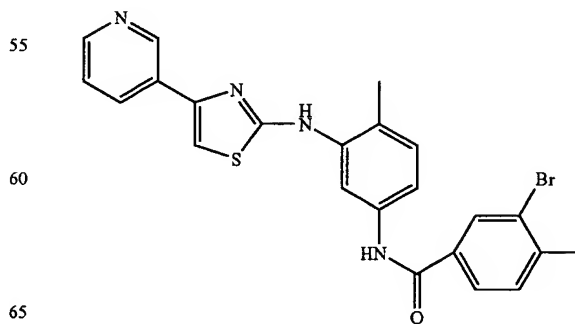
101: 4-[3-(2-Iodo-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



102: 4-[3-(4-Fluoro-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

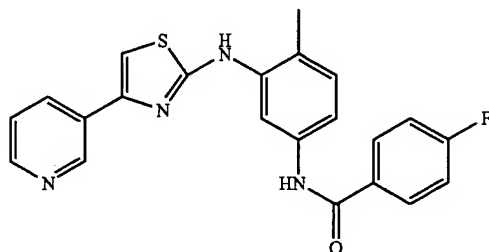


105: 3-Bromo-4-methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

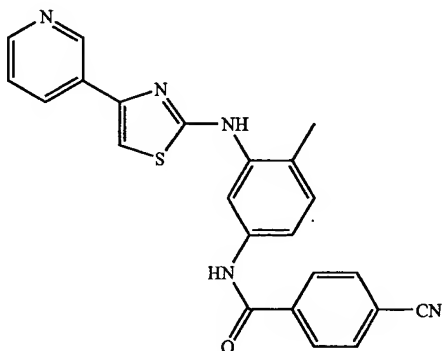


39

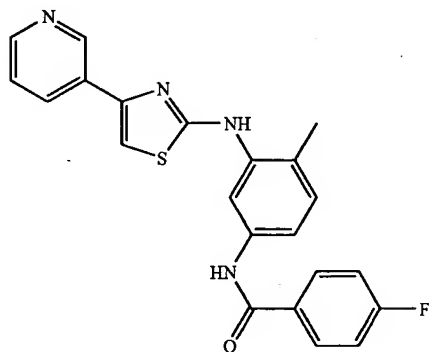
106: 4-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



103: 4-Cyano-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



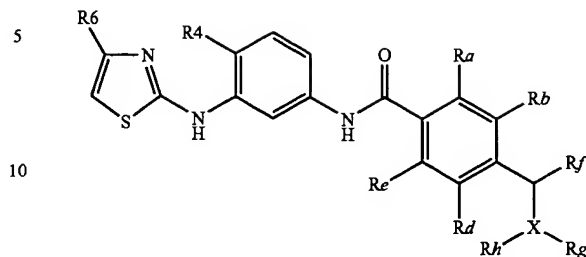
104: 4-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



Among compounds of formula II, the invention is particularly embodied by the compounds wherein X is a substituted-aryl group, corresponding to the 4-(4-substituted-1-ylmethyl)-N-[3-(thiazol-2-ylamino)-phenyl]-benzamide family and the following formula II-4:

40

FORMULA II-4



wherein X is a heteroatom, such as O or N

wherein Ra, Rb, Rd, Re, Rf, Rg, Rh are independently chosen from H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

or a NRR' group where R and R' are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

or an OR group where R is H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; a —SO<sub>2</sub>-R' group wherein R' is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

or a NRaCORb group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with

an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a NRaCONRbRc group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

or a COOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

or a CONRaRb, where Ra and Rb are a hydrogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

or an NHCOOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

an OSO<sub>2</sub>R, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

or an NRaOSO<sub>2</sub>Rb, where Ra and Rb are a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; Ra can also be a hydrogen; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

or a —SO<sub>2</sub>-R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a —CO—R or a —CO—NRR' group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

Ra, Rb, Rd, Re can also be halogen such as Cl, F, Br, I or trifluoromethyl;

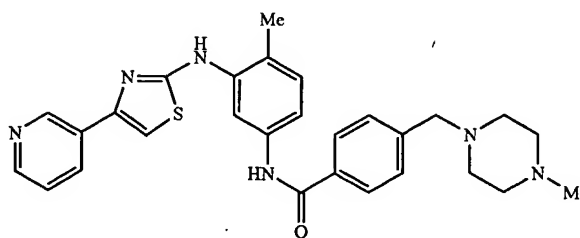
R<sup>4</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>6</sup> is one of the following:

- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- iv) H, a halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

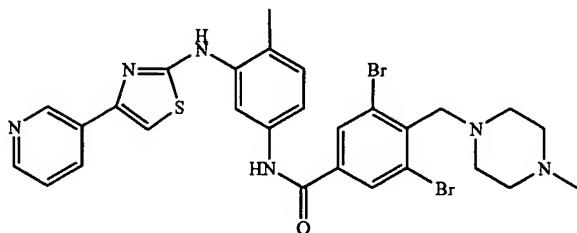
## EXAMPLES

066: 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

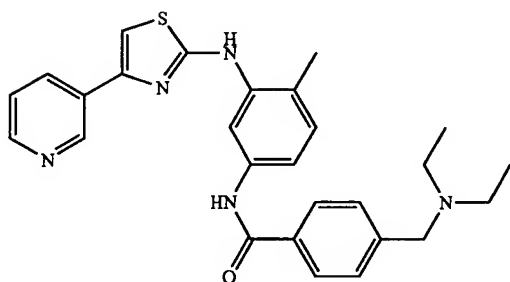


43

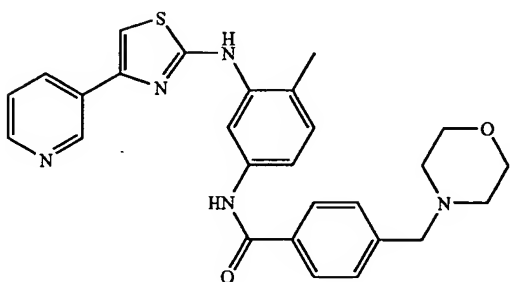
067: 3,5-Dibromo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



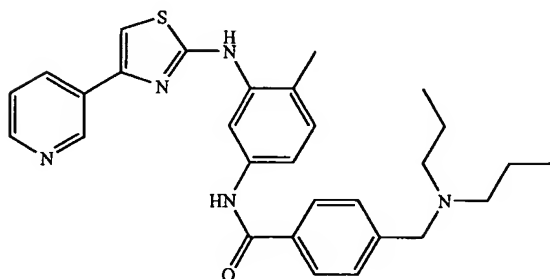
068: 4-Diethylaminomethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



069: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-morpholin-4-ylmethyl-benzamide

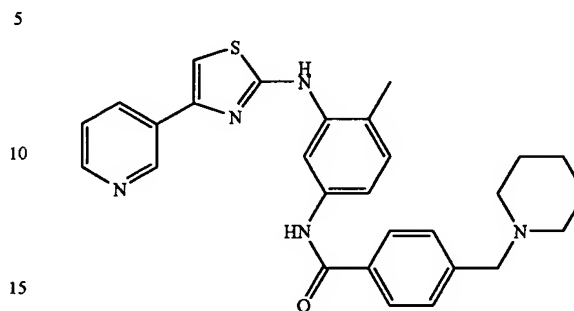


070: 4-Dipropylaminomethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

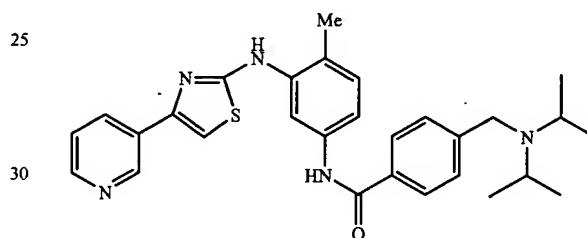


44

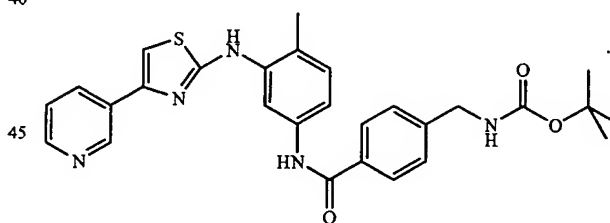
071: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-piperidin-1-ylmethyl-benzamide



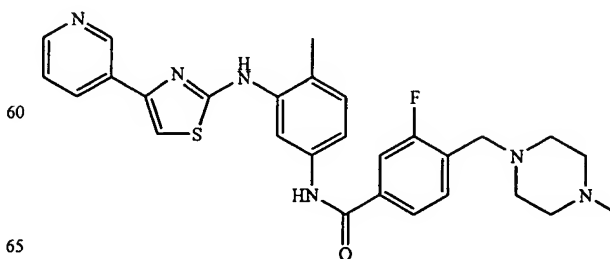
072: 4-[(Diisopropylamino)-methyl]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



073: {4-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-benzyl}-carbamic acid tert-butyl ester



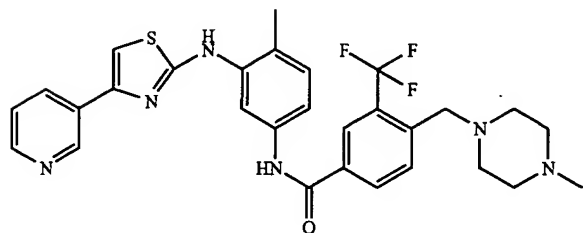
074: 3-Fluoro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide





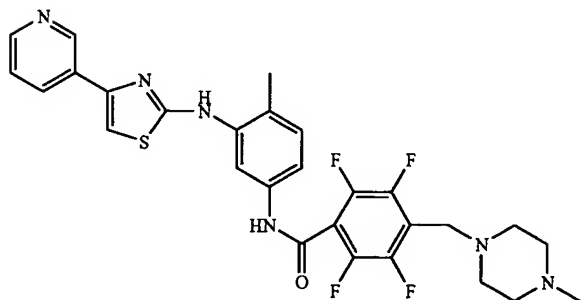
45

075: 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide

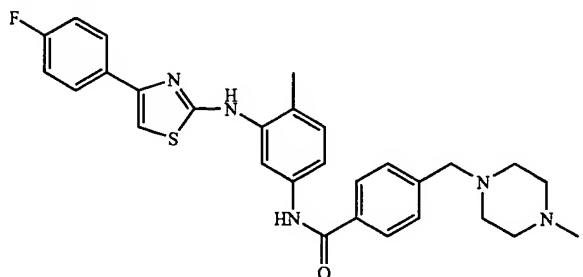


yellow crystals mp: 118-120° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.22 (s, 3H); 2.33 (s, 3H); 2.34-2.50 (m, 8H); 3.74 (s, 2H); 7.26 (d, J=8.3 Hz, 1H); 7.41-7.49 (m, 2H); 7.53 (s, 1H); 7.99 (d, J=8.0 Hz, 1H); 8.28-8.31 (m, 2H); 8.38 (d, J=7.9 Hz, 1H); 8.53 (dd, J=1.3 Hz, J=4.7 Hz, 1H); 8.68 (d, J=1.9 Hz, 1H); 9.21 (d, J=2.0 Hz, 1H); 9.53 (s, 1H); 10.49 (s, 1H)

076: 2,3,5,6-Tetrafluoro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

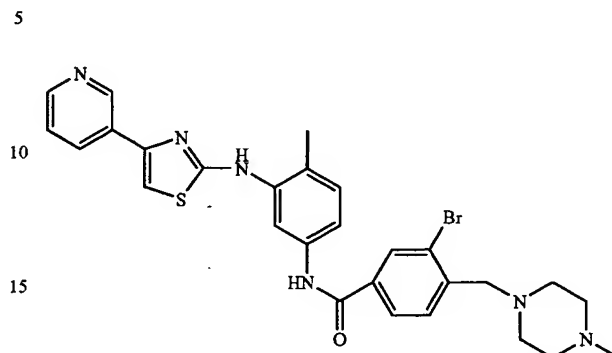


077: N-{3-[4-(4-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide

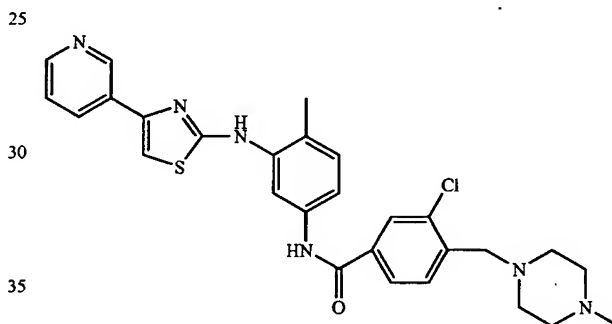


46

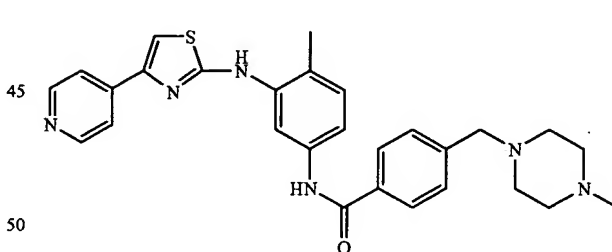
078: 3-Bromo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



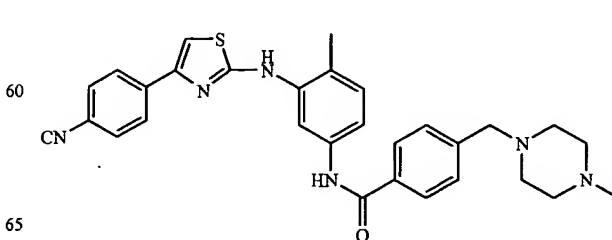
079: 3-Chloro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



080: 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-4-yl-thiazol-2-ylamino)-phenyl]-benzamide

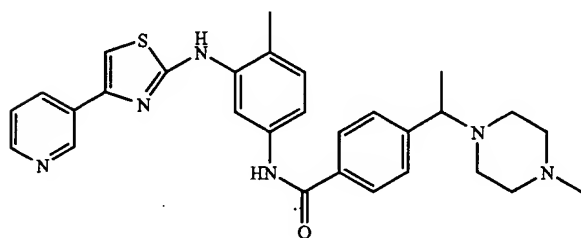


081: N-{3-[4-(4-Cyano-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



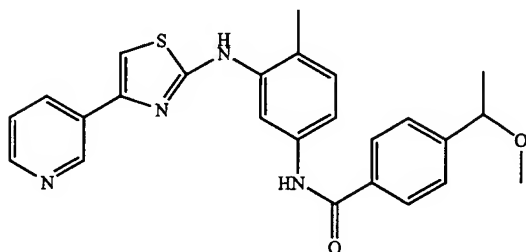
47

082: 4-[1-(4-Methyl-piperazin-1-yl)-ethyl]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

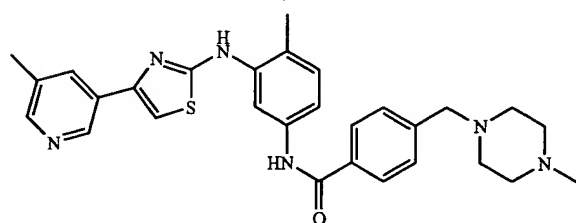


beige powder mp: 153-155° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>)  
 $\delta$ =1.29 (d, J=6.6 Hz, 3H); 2.15 (s, 3H); 2.26 (s, 3H); 3.15-3.25 (m, 9H); 7.18 (d, J=8.4 Hz, 1H); 7.35-7.47 (m, 5H); 7.91 (d, J=8.2 Hz, 2H); 8.31 (d, J=8.0 Hz, 1H); 8.47 (dd, J=1.6 Hz, J=4.7 Hz, 1H); 8.60 (d, J=2.0, 1H); 9.15 (d, J=0.6, 1H); 9.45 (s, 1H); 10.18 (s, 1H)

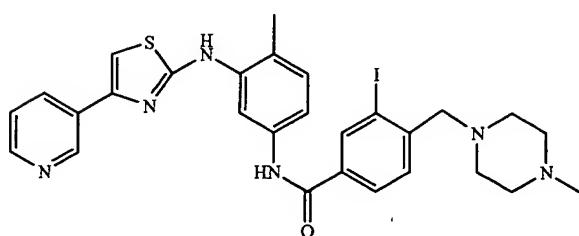
083: 4-(1-Methoxy-ethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



084: N-{4-Methyl-3-[4-(5-methyl-pyridin-3-yl)-thiazol-2-ylamino]-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide

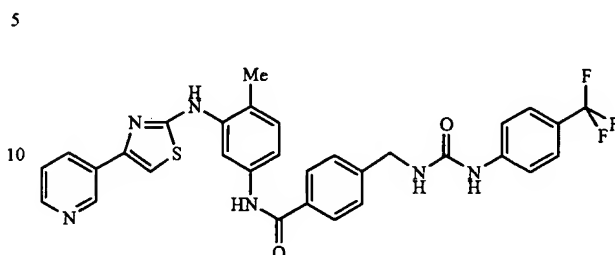


085: 3-Iodo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

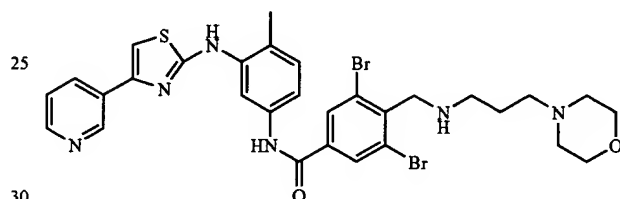


48

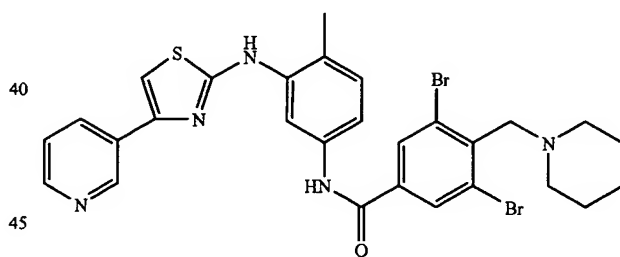
086: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[3-(4-trifluoromethyl-phenyl)-ureidomethyl]-benzamide



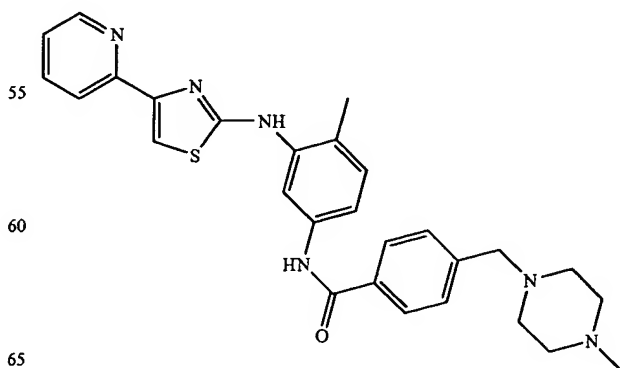
087: 3,5-Dibromo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[(3-morpholin-4-yl-propylamino)-methyl]-benzamide



107: 3,5-Dibromo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-piperidin-1-ylmethyl-benzamide

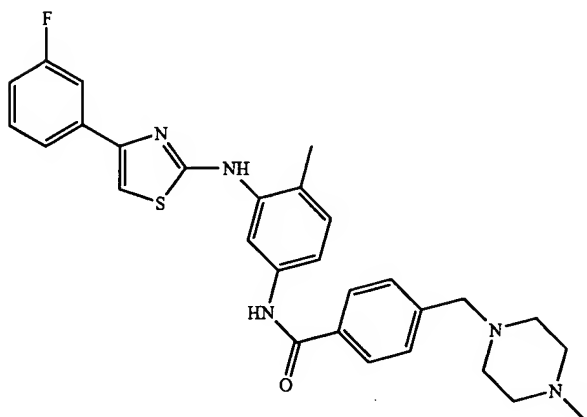


122: 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-2-yl-thiazol-2-ylamino)-phenyl]-benzamide

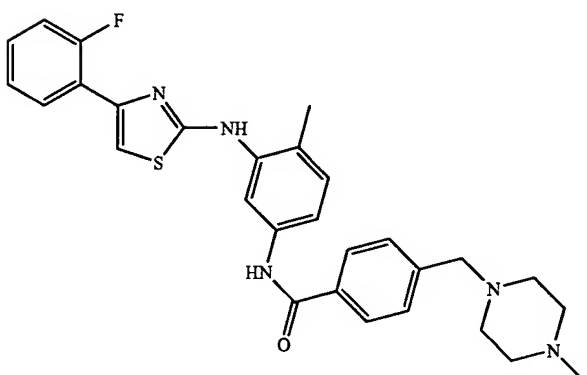


49

111: N-{3-[4-(3-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide

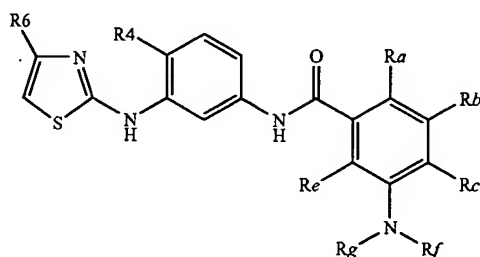


118: N-{3-[4-(2-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



Among compounds of formula II, the invention is particularly embodied by the compounds wherein X is a-aryl-substituted group, corresponding to the 3-Disubstituted-amino-N-[3-(thiazol-2-ylamino)-phenyl]-benzamide family and the following formula II-5:

FORMULA II-5



wherein Ra, Rb, Rc, Re, Rf, Rg are independently chosen from H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a

50

cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

or a NRR' group where R and R' are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or an OR group where R is H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; a —SO<sub>2</sub>-R' group wherein R' is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

or a NRaCORb group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a NRaCONRbRc group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

or a COOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom,

notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

or a CONRaRb, where Ra and Rb are a hydrogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

or an NHCOOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

an OSO<sub>2</sub>R, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

or an NRaOSO<sub>2</sub>Rb, where Ra and Rb are a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; Ra can also be a hydrogen; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

or a —SO<sub>2</sub>-R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a —CO—R or a —CO—NRR' group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at

least one heteroatom, notably selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality. Ra, Rb, Rc, Re can also be halogen such as Cl, F, Br, I or trifluoromethyl;

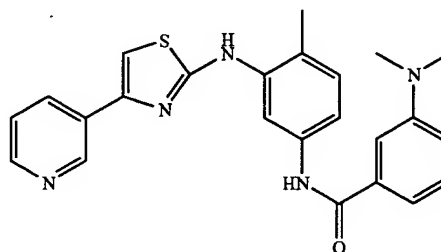
R<sup>4</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>6</sup> is one of the following:

- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- iv) H, a halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

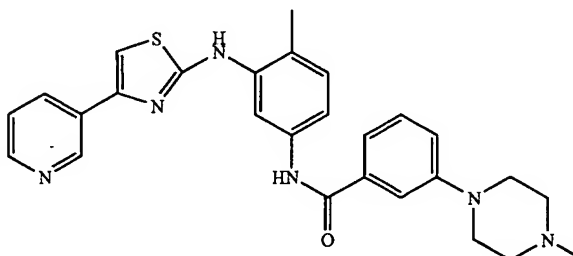
## EXAMPLES

088: 3-Dimethylamino-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



beige powder mp: 197-198° C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ=2.32 (s, 3H); 3.03 (s, 6H); 6.97 (d, J=6.4 Hz, 1H); 7.23-7.56 (m, 7H); 8.37 (d, J=7.3 Hz, 1H); 8.53 (d, J=4.7 Hz, 1H); 8.63 (s, 1H); 9.20 (s, 1H); 9.48 (s, 1H); 10.15 (s, 1H)

089: 3-(4-Methyl-piperazin-1-yl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

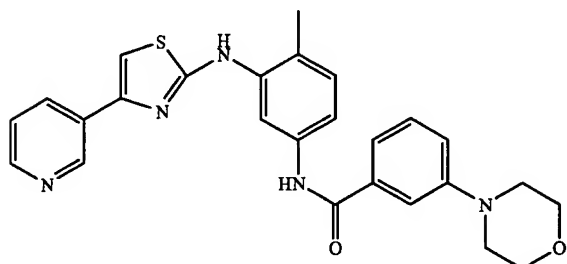


beige powder mp: 274-246° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>): δ=2.23 (s, 3H); 2.24-2.30 (m, 4H); 3.22-3.27 (m, 4H); 7.07-

53

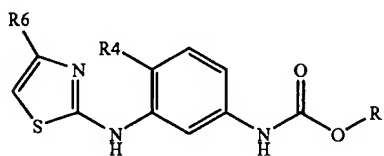
7.20 (m, 2H); 7.36-7.53 (m, 6H); 8.31 (d, J=7.5 Hz, 1H); 8.47 (d, J=3.7 Hz, 1H) 8.58 (s, 1H); 9.12 (d, J=7.8 Hz, 1H); 9.44 (s, 1H); 10.12 (s, 1H)

090: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-morpholin-4-yl-benzamide



beige powder mp: 247-248° C. <sup>1</sup>H RMN (CDCl<sub>3</sub>) δ=1.50 (s, 3H); 3.15-3.18 (m, 4H); 3.79-3.82 (m, 3H); 6.85 (s, 1H); 7.00-7.30 (m, 7H); 7.41 (s, 1H); 7.75 (s, 1H); 8.08 (d, J=7.9 Hz, 1H); 8.22 (d, J=1.7 Hz, 1H); 8.46 (dd, J=1.3 Hz, J=4.7 Hz, 1H); 9.01 (d, J=1.6 Hz, 1H)

Among the compounds of formula II, the invention is particularly embodied by the compounds wherein X is a —OR group, corresponding to the family [3-(Thiazol-2-ylamino)-phenyl]-carbamate and the following formula II-6



FORMULA II-6

wherein R is independently chosen from an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality;

R<sup>4</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>6</sup> is one of the following:

- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combi-

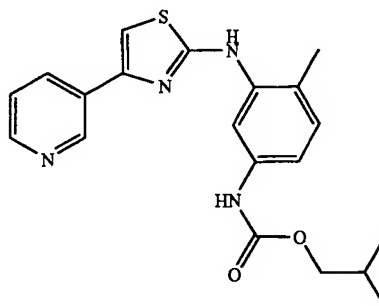
54

nation of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

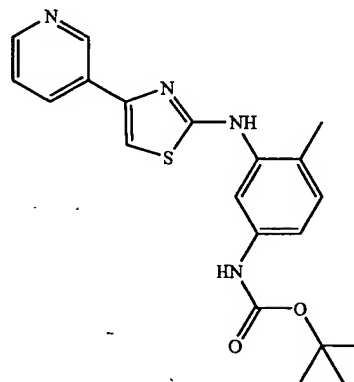
- iv) H, a halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

## EXAMPLES

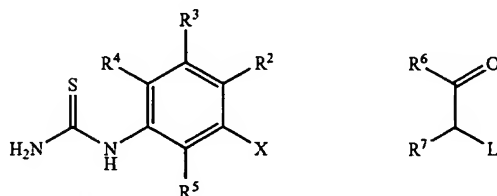
097: [4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-carbamic acid isobutyl ester



098: [4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-carbamic acid tert-butyl ester



In a second embodiment, the invention is directed to a process for manufacturing a compound of formula I depicted above. This entails the condensation of a substrate of general formula 10 with a thiourea of the type 11a-11d.



11 a: X = NH—R<sup>1</sup>

11 b: X = NH<sub>2</sub>

11 c: X = NH—PG

11 d: X = NO<sub>2</sub>

10

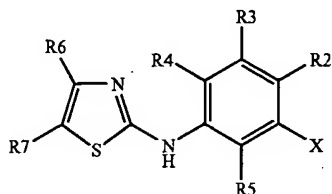
55

Substituent "L" in formula 10 is a leaving group suitable in nucleophilic substitution reactions (for example, L can be selected from chloro, bromo, iodo, toluenesulfonyloxy, methanesulfonyloxy, trifluoromethanesulfonyloxy, etc., with L being preferentially a bromo group).

Group R1 in formula 11a corresponds to group R1 as described in formula I.

Group "PG" in formula 11c is a suitable protecting group of a type commonly utilized by the person skilled in the art.

The reaction of 10 with 1 a-d leads to a thiozole-type product of formula 12a-d.



12 a: X = NH—R1  
12 b: X = NH2  
12 c: X = NH—PG  
12 d: X = NO2

Formula 12a is the same as formula I. Therefore, R1 in 12a corresponds to R1 in formula I.

Formula 12b describes a precursor to compounds of formula I which lack substituent R1. Therefore, in a second phase of the synthesis, substituent R1 is connected to the free amine group in 12b, leading to the complete structure embodied by formula I:

12b+ "R1" → I

The introduction of R1, the nature of which is as described on page 3 for the general formula I, is achieved by the use of standard reactions that are well known to the person skilled in the art, such as alkylation, acylation, sulfonylation, formation of ureas, etc.

Formula 12c describes an N-protected variant of compound 12b. Group "PG" in formula 12c represents a protecting group of the type commonly utilized by the person skilled in the art. Therefore, in a second phase of the synthesis, group PG is cleaved to transform compound 12c into compound 12b. Compound 12b is subsequently advanced to structures of formula I as detailed above.

Formula 12d describes a nitro analogue of compound 12b. In a second phase of the synthesis, the nitro group of compound 12d is reduced by any of the several methods utilized by the person skilled in the art to produce the corresponding amino group, namely compound 12b. Compound 12b thus obtained is subsequently advanced to structures of formula I as detailed above.

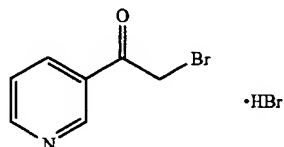
#### Examples of Compound Synthesis

General: All chemicals used were commercial reagent grade products. Dimethylformamide (DMF), methanol (MeOH) were of anhydrous commercial grade and were used without further purification. Dichloromethane and tetrahydrofuran (THF) were freshly distilled under a stream of argon before use. The progress of the reactions was monitored by thin layer chromatography using precoated silica gel 60F 254, Fluka TLC plates, which were visualized under UV light. Multiplicities in <sup>1</sup>H NMR spectra are indicated as singlet (s),

56

broad singlet (br s), doublet (d), triplet (t), quadruplet (q), and multiplet (m) and the NMR spectrum were realized on a 300 MHz Bruker spectrometer.

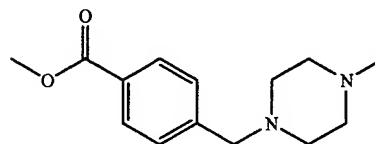
#### 3-Bromoacetyl-pyridine, HBr Salt



Dibromine (17.2 g, 108 mmol) was added dropwise to a cold (0° C.) solution of 3-acetyl-pyridine (12 g, 99 mmol) in acetic acid containing 33% of HBr (165 mL) under vigorous stirring. The vigorously stirred mixture was warmed to 40° C. for 2 h and then to 75° C. After 2 h at 75° C., the mixture was cooled and diluted with ether (400 mL) to precipitate the product, which was recovered by filtration and washed with ether and acetone to give white crystals (100%). This material may be recrystallised from methanol and ether.

IR (neat): 3108, 2047, 2982, 2559, 1709, 1603, 1221, 1035, 798 cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ=5.09 (s, 2H, CH<sub>2</sub>Br); 7.88 (m, 1H, pyridyl-H); 8.63 (m, 1H, pyridyl-H); 8.96 (m, 1H, pyridyl-H); 9.29 (m, 1H, pyridyl-H).

#### Methyl-[4-(1-N-methyl-piperazino)-methyl]-benzoate

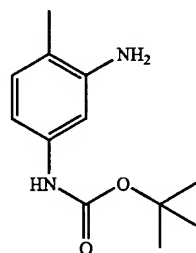


To methyl-4-formyl benzoate (4.92 g, 30 mmol) and N-methyl-piperazine (3.6 mL, 32 mmol) in acetonitrile (100 mL) was added dropwise 2.5 mL of trifluoroacetic acid. The reaction mixture was stirred at room temperature for 1 h. After slow addition of sodium cyanoborohydride (2 g, 32 mmol), the solution was left stirring overnight at room temperature. Water (10 mL) was then added to the mixture, which was further acidified with 1N HCl to pH=6-7. The acetonitrile was removed under reduced pressure and the residual aqueous solution was extracted with diethyl ether (4x30 mL). These extracts were discarded. The aqueous phase was then basified (pH>12) by addition of 2.5N aqueous sodium hydroxide solution. The crude product was extracted with ethyl acetate (4x30 mL). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated under reduced pressure to afford a slightly yellow oil which became colorless after purification by Kugelrohr distillation (190° C.) in 68% yield.

IR (neat): 3322, 2944, 2802, 1721, 1612, 1457, 1281, 1122, 1012 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ=2.27 (s, 3H, NCH<sub>3</sub>); 2.44 (m, 8H, 2xNCH<sub>2</sub>CH<sub>2</sub>N); 3.53 (s, 2H, ArCH<sub>2</sub>N); 3.88 (s, 3H, OCH<sub>3</sub>); 7.40 (d, 2H, J=8.3 Hz, 2xArH); 7.91 (d, 2H, J=8.3 Hz, 2xArH). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ=45.8 (NCH<sub>3</sub>); 51.8 (OCH<sub>3</sub>); 52.9 (2xCH<sub>2</sub>N); 54.9 (2xCH<sub>2</sub>N); 62.4 (ArCH<sub>2</sub>N); 128.7 (2xArC); 129.3 (2xArC); 143.7 (ArC); 166.7 (ArCO<sub>2</sub>CH<sub>3</sub>). MS Cl (m/z) (%) 249 (M+1, 100%).

57

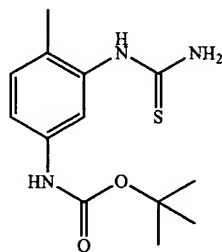
## 2-Methyl-5-tert-butoxycarbonylamino-aniline



A solution of di-tert-butylidicarbonate (70 g, 320 mmol) in methanol (200 mL) was added over 2 h to a cold ( $-10^{\circ}\text{C}$ .) solution of 2,4-diaminotoluene (30 g, 245 mmol) and triethylamine (30 mL) in methanol (15 mL). The reaction was followed by thin layer chromatography (hexane/ethyl acetate, 3:1) and stopped after 4 h by adding 50 mL of water. The mixture was concentrated in vacuo and the residue was dissolved in 500 mL of ethyl acetate. This organic phase was washed with water (1x150 mL) and brine (2x150 mL), dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure. The resulting light brown solid was washed with small amounts of diethyl ether to give off-white crystals of 2-methyl-5-tert-butoxycarbonylamino-aniline in 67% yield.

IR (neat): 3359; 3246; 2970; 1719; 1609; 1557; 1173; 1050  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$ =1.50 (s, 9H, tBu); 2.10 (s, 3H,  $\text{ArCH}_3$ ); 3.61 (br s, 2H,  $\text{NH}_2$ ); 6.36 (br s, 1H, NH); 6.51 (dd, 1H,  $J$ =7.9 Hz, 2.3 Hz, ArH); 6.92 (d, 1H,  $J$ =7.9 Hz, ArH); 6.95 (s, 1H, ArH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$ =16.6 ( $\text{ArCH}_3$ ); 28.3 ( $\text{C}(\text{CH}_3)_3$ ); 80.0 ( $\text{C}(\text{CH}_3)_3$ ); 105.2 (ArC); 108.6 (ArC); 116.9 (ArC); 130.4 ( $\text{ArC}-\text{CH}_3$ ); 137.2 ( $\text{ArC}-\text{NH}$ ); 145.0 ( $\text{ArC}-\text{NH}_2$ ); 152.8 ( $\text{COOtBu}$ ) MS ESI ( $m/z$ ) (%): 223 ( $M+1$ ), 167 (55, 100%).

## N-(2-methyl-5-tert-butoxycarbonylamino)phenyl-thiourea



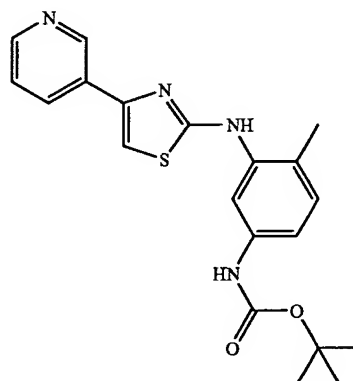
Benzoyl chloride (5.64 g, 80 mmol) was added dropwise to a well-stirred solution of ammonium thiocyanate (3.54 g, 88 mmol) in acetone (50 mL). The mixture was refluxed for 15 min, then, the hydrobromide salt of 2-methyl-5-tert-butoxycarbonylamino-aniline (8.4 g, 80 mmol) was added slowly portionwise. After 1 h, the reaction mixture was poured into ice-water (350 mL) and the bright yellow precipitate was isolated by filtration. This crude solid was then refluxed for 45 min in 70 mL of 2.5 N sodium hydroxide solution. The

58

mixture was cooled down and basified with ammonium hydroxide. The precipitate of crude thiourea was recovered by filtration and dissolved in 150 mL of ethyl acetate. The organic phase was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate, 1:1) to afford 63% of N-(2-methyl-5-tert-butoxycarbonylamino)phenyl-thiourea as a white solid.

IR (neat): 3437, 3292, 3175, 2983, 1724, 1616, 1522, 1161, 1053  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$ =1.46 (s, 9H, tBu); 2.10 (s, 3H,  $\text{ArCH}_3$ ); 3.60 (br s, 2H,  $\text{NH}_2$ ); 7.10 (d, 1H,  $J$ =8.29 Hz, ArH); 7.25 (d, 1H,  $J$ =2.23 Hz, ArH); 7.28 (d, 1H,  $J$ =2.63 Hz, ArH); 9.20 (s, 1H, ArNH); 9.31 (s, 1H, ArNH).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$ =25.1 ( $\text{ArCH}_3$ ); 28.1 ( $\text{C}(\text{CH}_3)_3$ ); 78.9 ( $\text{C}(\text{CH}_3)_3$ ); 16.6 (ArC); 117.5 (ArC); 128.0 (ArC); 130.4 ( $\text{ArC}-\text{CH}_3$ ); 136.5 ( $\text{ArC}-\text{NH}$ ); 137.9 ( $\text{ArC}-\text{NH}$ ); 152.7 ( $\text{COOtBu}$ ); 181.4 ( $\text{C}=\text{S}$ ). MS Cl( $m/z$ ): 282 ( $M+1$ , 100%); 248 (33); 226 (55); 182 (99); 148 (133); 93 (188).

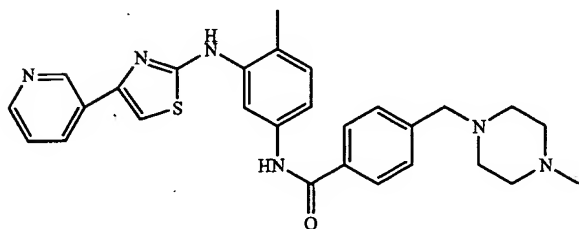
## 2-(2-methyl-5-tert-butoxycarbonylamino)phenyl-4-(3-pyridyl)-thiazole



A mixture of 3-bromoacetyl-pyridine, HBr salt (0.81 g, 2.85 mmol), N-(2-methyl-5-tert-butoxycarbonylamino)phenyl-thiourea (0.8 g, 2.85 mmol) and  $\text{KHCO}_3$  (0.4 g) in ethanol (40 mL) was heated at  $75^{\circ}\text{C}$ . for 20 h. The mixture was cooled, filtered (removal of  $\text{KHCO}_3$ ) and evaporated under reduced pressure. The residue was dissolved in  $\text{CHCl}_3$  (40 mL) and washed with saturated aqueous sodium hydrogen carbonate solution and with water. The organic layer was dried over  $\text{Na}_2\text{SO}_4$  and concentrated. Column chromatographic purification of the residue (hexane/ethyl acetate, 1:1) gave the desired thiazole in 70% yield as an orange solid.

IR (neat): 3380, 2985, 2942, 1748, 1447, 1374, 1239, 1047, 938  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$ =1.53 (s, 9H, tBu); 2.28 (s, 3H,  $\text{ArCH}_3$ ); 6.65 (s, 1H, thiazole-H); 6.89 (s, 1H); 6.99 (dd, 1H,  $J$ =8.3 Hz, 2.3 Hz); 7.12 (d, 2H,  $J$ =8.3 Hz); 7.35 (dd, 1H,  $J$ =2.6 Hz, 4.9 Hz); 8.03 (s, 1H); 8.19 (dt, 1H,  $J$ =1.9 Hz, 7.9 Hz); 8.54 (br s, 1H, NH); 9.09 (s, 1H, NH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$ =18.02 ( $\text{ArCH}_3$ ); 29.2 ( $\text{C}(\text{CH}_3)_3$ ); 81.3 ( $\text{C}(\text{CH}_3)_3$ ); 104.2 (thiazole-C); 111.6; 115.2; 123.9; 124.3; 131.4; 132.1; 134.4; 139.5; 148.2; 149.1; 149.3; 153.6; 167.3 ( $\text{C}=\text{O}$ ). MS Cl( $m/z$ ) (%): 383 ( $M+1$ , 100%); 339 (43); 327 (55); 309 (73); 283 (99); 71 (311).

## 2-(2-methyl-5-amino)phenyl-4-(3-pyridyl)-thiazole



2-(2-methyl-5-tert-butoxycarbonylamino)phenyl-4-(3-pyridyl)-thiazole (0.40 g, 1.2 mmol) was dissolved in 10 mL of 20% TFA/CH<sub>2</sub>Cl<sub>2</sub>. The solution was stirred at room temperature for 2 h, then it was evaporated under reduced pressure. The residue was dissolved in ethyl acetate. The organic layer was washed with aqueous 1N sodium hydroxide solution, dried over MgSO<sub>4</sub>, and concentrated to afford 2-(2-methyl-5-amino)phenyl-4-(3-pyridyl)-thiazole as a yellow-orange solid in 95% yield. This crude product was used directly in the next step.

A 2M solution of trimethyl aluminum in toluene (2.75 mL) was added dropwise to a cold (0° C.) solution of 2-(2-methyl-5-amino)phenyl-4-(3-pyridyl)-thiazole (0.42 g, 1.5 mmol) in anhydrous dichloromethane (10 mL) under argon atmosphere. The mixture was warmed to room temperature and stirred at room temperature for 30 min. A solution of methyl 4-(1-N-methyl-piperazino)-methyl benzoate (0.45 g, 1.8 mmol) in anhydrous dichloromethane (1 mL) and added slowly, and the resulting mixture was heated at reflux for 5 h. The mixture was cooled to 0° C. and quenched by dropwise addition of a 4N aqueous sodium hydroxide solution (3 mL). The mixture was extracted with dichloromethane (3×20 mL). The combined organic layers were washed with brine (3×20 mL) and dried over anhydrous MgSO<sub>4</sub>. 2-(2-methyl-5-amino)phenyl-4-(3-pyridyl)-thiazole is obtained in 72% after purification by column chromatography (dichloromethane/methanol, 3:1).

IR (neat): 3318, 2926, 1647, 1610, 1535, 1492, 1282, 1207, 1160, 1011, 843—<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ=2.31 (br s, 6H, ArCH<sub>3</sub>+NCH<sub>3</sub>); 2.50 (br s, 8H, 2×NCH<sub>2</sub>CH<sub>2</sub>N); 3.56 (s, 2H, ArCH<sub>2</sub>N); 6.89 (s, 1H, thiazoleH); 7.21-7.38 (m, 4H); 7.45 (m, 2H); 7.85 (d, 2H, J=8.3 Hz); 8.03 (s, 1H); 8.13 (s, 1H); 8.27 (s, 1H); 8.52 (br s, 1H); 9.09 (s, 1H, NH)—<sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 17.8 (ArCH<sub>3</sub>); 46.2 (NCH<sub>3</sub>); 53.3 (NCH<sub>2</sub>); 55.3 (NCH<sub>2</sub>); 62.8 (ArCH<sub>2</sub>N); 99.9 (thiazole-C); 112.5; 123.9; 125.2; 127.5; 129.6; 131.6; 133.7; 134.0; 137.6; 139.3; 142.9; 148.8; 149.1; 166.2 (C=O); 166.7 (thiazoleC-NH)—MS CI (m/z) (%): 499 (M+H, 100%); 455 (43); 430 (68); 401 (97); 374 (124); 309 (189); 283 (215); 235 (263); 121 (377); 99 (399).

In a third embodiment, the invention relates to a pharmaceutical composition comprising a compound as depicted above.

Such medicament can take the form of a pharmaceutical composition adapted for oral administration, which can be formulated using pharmaceutically acceptable carriers well known in the art in suitable dosages. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient. In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries which facilitate pro-

cessing of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, Pa.).

The composition of the invention can also take the form of a pharmaceutical or cosmetic composition for topical administration.

Such compositions may be presented in the form of a gel, paste, ointment, cream, lotion, liquid suspension aqueous, aqueous-alcoholic or, oily solutions, or dispersions of the lotion or serum type, or anhydrous or lipophilic gels, or emulsions of liquid or semi-solid consistency of the milk type, obtained by dispersing a fatty phase in an aqueous phase or vice versa, or of suspensions or emulsions of soft, semi-solid consistency of the cream or gel type, or alternatively of microemulsions, of microcapsules, of microparticles or of vesicular dispersions to the ionic and/or nonionic type. These compositions are prepared according to standard methods.

The composition according to the invention comprises any ingredient commonly used in dermatology and cosmetic. It may comprise at least one ingredient selected from hydrophilic or lipophilic gelling agents, hydrophilic or lipophilic active agents, preservatives, emollients, viscosity enhancing polymers, humectants, surfactants, preservatives, antioxidants, solvents, and fillers, antioxidants, solvents, perfumes, fillers, screening agents, bactericides, odor absorbers and coloring matter.

As oils which can be used in the invention, mineral oils (liquid paraffin), vegetable oils (liquid fraction of shea butter, sunflower oil), animal oils, synthetic oils, silicone oils (cyclomethicone) and fluorinated oils may be mentioned. Fatty alcohols, fatty acids (stearic acid) and waxes (paraffin, carnauba, beeswax) may also be used as fatty substances.

As emulsifiers which can be used in the invention, glycerol stearate, polysorbate 60 and the PEG-6/PEG-32/glycol stearate mixture are contemplated.

As hydrophilic gelling agents, carboxyvinyl polymers (carbomer), acrylic copolymers such as acrylate/alkylacrylate copolymers, polyacrylamides, polysaccharides such as hydroxypropylcellulose, clays and natural gums may be mentioned, and as lipophilic gelling agents, modified clays such as bentones, metal salts of fatty acids such as aluminum stearates and hydrophobic silica, or alternatively ethylcellulose and polyethylene may be mentioned.

As hydrophilic active agents, proteins or protein hydrolysates, amino acids, polyols, urea, allantoin, sugars and sugar derivatives, vitamins, starch and plant extracts, in particular those of Aloe vera may be used.

As lipophilic active agents, retinol (vitamin A) and its derivatives, tocopherol (vitamin E) and its derivatives, essential fatty acids, ceramides and essential oils may be used. These agents add extra moisturizing or skin softening features when utilized.

In addition, a surfactant can be included in the composition so as to provide deeper penetration of the compound capable of depleting mast cells, such as a tyrosine kinase inhibitor, preferably a c-kit inhibitor.

Among the contemplated ingredients, the invention embraces penetration enhancing agents selected for example from the group consisting of mineral oil, water, ethanol, triacetin, glycerin and propylene glycol; cohesion agents selected for example from the group consisting of polyisobutylene, polyvinyl acetate and polyvinyl alcohol, and thickening agents.

Chemical methods of enhancing topical absorption of drugs are well known in the art.



For example, compounds with penetration enhancing properties include sodium lauryl sulfate (Dugard, P. H. and Sheuplein, R. J., "Effects of Ionic Surfactants on the Permeability of Human Epidermis: An Electrometric Study," *J. Invest. Dermatol.*, V.60, pp. 263-69, 1973), lauryl amine oxide (Johnson et. al., U.S. Pat. No. 4,411,893), azone (Rajadhyaksha, U.S. Pat. Nos. 4,405,616 and 3,989,816) and decylmethyl sulfoxide (Sekura, D. L. and Scala, J., "The Percutaneous Absorption of Alkylmethyl Sulfides," *Pharmacology of the Skin, Advances In Biology of Skin*, (Appleton-Century Craft) V. 12, pp. 257-69, 1972). It has been observed that increasing the polarity of the head group in amphoteric molecules increases their penetration-enhancing properties but at the expense of increasing their skin irritating properties (Cooper, E. R. and Berner, B., "Interaction of Surfactants with Epidermal Tissues: Physicochemical Aspects," *Surfactant Science Series*, V. 16, Reiger, M. M. ed. (Marcel Dekker, Inc.) pp. 195-210, 1987).

A second class of chemical enhancers are generally referred to as co-solvents. These materials are absorbed topically relatively easily, and, by a variety of mechanisms, achieve permeation enhancement for some drugs. Ethanol (Gale et. al., U.S. Pat. No. 4,615,699 and Campbell et. al., U.S. Pat. Nos. 4,460,372 and 4,379,454), dimethyl sulfoxide (U.S. Pat. Nos. 3,740,420 and 3,743,727, and U.S. Pat. No. 4,575,515), and glycerine derivatives (U.S. Pat. No. 4,322,433) are a few examples of compounds which have shown an ability to enhance the absorption of various compounds.

The pharmaceutical compositions of the invention can also be intended for administration with aerosolized formulation to target areas of a patient's respiratory tract.

Devices and methodologies for delivering aerosolized bursts of a formulation of a drug is disclosed in U.S. Pat. No. 5,906,202. Formulations are preferably solutions, e.g. aqueous solutions, ethanoic solutions, aqueous/ethanoic solutions, saline solutions, colloidal suspensions and microcrystalline suspensions. For example aerosolized particles comprise the active ingredient mentioned above and a carrier, (e.g., a pharmaceutically active respiratory drug and carrier) which are formed upon forcing the formulation through a nozzle which nozzle is preferably in the form of a flexible porous membrane. The particles have a size which is sufficiently small such that when the particles are formed they remain suspended in the air for a sufficient amount of time such that the patient can inhale the particles into the patient's lungs.

The invention encompasses the systems described in U.S. Pat. No. 5,556,611:

- liquid gas systems (a liquefied gas is used as propellant gas (e.g. low-boiling FCHC or propane, butane) in a pressure container,
- suspension aerosol (the active substance particles are suspended in solid form in the liquid propellant phase),
- pressurized gas system (a compressed gas such as nitrogen, carbon dioxide, dinitrogen monoxide, air is used.

Thus, according to the invention the pharmaceutical preparation is made in that the active substance is dissolved or dispersed in a suitable nontoxic medium and said solution or dispersion atomized to an aerosol, i.e. distributed extremely finely in a carrier gas. This is technically possible for example in the form of aerosol propellant gas packs, pump aerosols or other devices known per se for liquid misting and solid atomizing which in particular permit an exact individual dosage.

Therefore, the invention is also directed to aerosol devices comprising the compound as defined above and such a formulation, preferably with metered dose valves.

The pharmaceutical compositions of the invention can also be intended for intranasal administration.

In this regard, pharmaceutically acceptable carriers for administering the compound to the nasal mucosal surfaces will be readily appreciated by the ordinary artisan. These carriers are described in the Remington's *Pharmaceutical Sciences* 16th edition, 1980, Ed. By Arthur Osol, the disclosure of which is incorporated herein by reference.

The selection of appropriate carriers depends upon the particular type of administration that is contemplated. For administration via the upper respiratory tract, the composition can be formulated into a solution, e.g., water or isotonic saline, buffered or unbuffered, or as a suspension, for intranasal administration as drops or as a spray. Preferably, such solutions or suspensions are isotonic relative to nasal secretions and of about the same pH, ranging e.g., from about pH 4.0 to about pH 7.4 or, from pH 6.0 to pH 7.0. Buffers should be physiologically compatible and include, simply by way of example, phosphate buffers. For example, a representative nasal decongestant is described as being buffered to a pH of about 6.2 (Remington's, Id. at page 1445). Of course, the ordinary artisan can readily determine a suitable saline content and pH for an innocuous aqueous carrier for nasal and/or upper respiratory administration.

Common intranasal carriers include nasal gels, creams, pastes or ointments with a viscosity of, e.g., from about 10 to about 3000 cps, or from about 2500 to 6500 cps, or greater, may also be used to provide a more sustained contact with the nasal mucosal surfaces. Such carrier viscous formulations may be based upon, simply by way of example, alkylcelluloses and/or other biocompatible carriers of high viscosity well known to the art (see e.g., Remington's, cited supra. A preferred alkylcellulose is, e.g., methylcellulose in a concentration ranging from about 5 to about 1000 or more mg per 100 ml of carrier. A more preferred concentration of methyl cellulose is, simply by way of example, from about 25 to about mg per 100 ml of carrier.

Other ingredients, such as art known preservatives, colorants, lubricating or viscous mineral or vegetable oils, perfumes, natural or synthetic plant extracts such as aromatic oils, and humectants and viscosity enhancers such as, e.g., glycerol, can also be included to provide additional viscosity, moisture retention and a pleasant texture and odor for the formulation. For nasal administration of solutions or suspensions according to the invention, various devices are available in the art for the generation of drops, droplets and sprays.

A premeasured unit dosage dispenser including a dropper or spray device containing a solution or suspension for delivery as drops or as a spray is prepared containing one or more doses of the drug to be administered and is another object of the invention. The invention also includes a kit containing one or more unit dehydrated doses of the compound, together with any required salts and/or buffer agents, preservatives, colorants and the like, ready for preparation of a solution or suspension by the addition of a suitable amount of water.

Another aspect of the invention is directed to the use of said compound to manufacture a medicament. In other words, the invention embraces a method for treating a disease related to unregulated c-kit transduction comprising administering an effective amount of a compound as defined above to a mammal in need of such treatment.

More particularly, the invention is aimed at a method for treating a disease selected from autoimmune diseases, allergic diseases, bone loss, cancers such as leukemia and GIST, tumor angiogenesis, inflammatory diseases, inflammatory bowel diseases (IBD), interstitial cystitis, mastocytosis, infections diseases, metabolic disorders, fibrosis, diabetes

and CNS disorders comprising administering an effective amount of a compound depicted above to a mammal in need of such treatment.

The above described compounds are useful for manufacturing a medicament for the treatment of diseases related to unregulated c-kit transduction, including, but not limited to:

neoplastic diseases such as mastocytosis, canine mastocytoma, human gastrointestinal stromal tumor ("GIST"), small cell lung cancer, non-small cell lung cancer, acute myelocytic leukemia, acute lymphocytic leukemia, myelodysplastic syndrome, chronic myelogenous leukemia, colorectal carcinomas, gastric carcinomas, gastrointestinal stromal tumors, testicular cancers, glioblastomas, solid tumors and astrocytomas.

tumor angiogenesis.

metabolic diseases such as diabetes mellitus and its chronic complications; obesity; diabetes type II; hyperlipidemias and dyslipidemias; atherosclerosis; hypertension; and cardiovascular disease.

allergic diseases such as asthma, allergic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, angioedema, atopic dermatitis, allergic contact dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing vasculitis and insect bite skin inflammation and blood sucking parasitic infestation.

interstitial cystitis.

bone loss (osteoporosis).

inflammatory diseases such as rheumatoid arthritis, conjunctivitis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions.

autoimmune diseases such as multiple sclerosis, psoriasis, intestine inflammatory disease, ulcerative colitis, Crohn's disease, rheumatoid arthritis and polyarthritis, local and systemic scleroderma, systemic lupus erythematosus, discoid lupus erythematosus, cutaneous lupus, dermatomyositis, polymyositis, Sjogren's syndrome, nodular panarteritis, autoimmune enteropathy, as well as proliferative glomerulonephritis.

graft-versus-host disease or graft rejection in any organ transplantation including kidney, pancreas, liver, heart, lung, and bone marrow.

Other autoimmune diseases embraced by the invention active chronic hepatitis and chronic fatigue syndrome subepidermal blistering disorders such as pemphigus.

Vasculitis.

melanocyte dysfunction associated diseases such as hypermelanosis resulting from melanocyte dysfunction and including lentigines, solar and senile lentigo, Dubreuilh melanosis, moles as well as malignant melanomas. In this regard, the invention embraces the use of the compounds defined above to manufacture a medicament or a cosmetic composition for whitening human skin.

CNS disorders such as psychiatric disorders, migraine, pain, memory loss and nerve cells degeneracy. More particularly, the method according to the invention is useful for the treatment of the following disorders: Depression including dysthymic disorder, cyclothymic disorder, bipolar depression, severe or "melancholic" depression, a typical depression, refractory depression, seasonal depression, anorexia, bulimia, premenstrual syndrome, post-menopause syndrome, other syndromes such as mental slowing and loss of concentration, pessimistic worry, agitation, self-deprecation, decreased libido, pain including, acute pain, postoperative pain, chronic pain, nociceptive pain, cancer pain, neuropathic pain, psychogenic pain syndromes, anxiety disorders including anxiety associated with hyperventilation and

cardiac arrhythmias, phobic disorders, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, psychiatric emergencies such as panic attacks, including psychosis, delusional disorders, conversion disorders, phobias, mania, delirium, dissociative episodes including dissociative amnesia, dissociative fugue and dissociative identity disorder, depersonalization, catatonia, seizures, severe psychiatric emergencies including suicidal behaviour, self-neglect, violent or aggressive behaviour, trauma, borderline personality, and acute psychosis, schizophrenia including paranoid schizophrenia, disorganized schizophrenia, catatonic schizophrenia, and undifferentiated schizophrenia,

neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, Huntington's disease, the prion diseases, Motor Neurone Disease (MND), and Amyotrophic Lateral Sclerosis (ALS).

substance use disorders as referred herein include but are not limited to drug addiction, drug abuse, drug habituation, drug dependence, withdrawal syndrome and overdose.

Cerebral ischemia

Fibrosis

Duchenne muscular dystrophy

Regarding mastocytosis, the invention contemplates the use of the compounds as defined above for treating the different categories which can be classified as follows:

The category I is composed by two sub-categories (IA and IB). Category IA is made by diseases in which mast cell infiltration is strictly localized to the skin. This category represents the most frequent form of the disease and includes: i) urticaria pigmentosa, the most common form of cutaneous mastocytosis, particularly encountered in children, ii) diffuse cutaneous mastocytosis, iii) solitary mastocytoma and iv) some rare subtypes like bullous, erythrodermic and teleangiectatic mastocytosis. These forms are characterized by their excellent prognosis with spontaneous remissions in children and a very indolent course in adults. Long term survival of this form of disease is generally comparable to that of the normal population and the translation into another form of mastocytosis is rare. Category IB is represented by indolent systemic disease (SM) with or without cutaneous involvement. These forms are much more usual in adults than in children. The course of the disease is often indolent, but sometimes signs of aggressive or malignant mastocytosis can occur, leading to progressive impaired organ function.

The category II includes mastocytosis with an associated hematological disorder, such as a myeloproliferative or myelodysplastic syndrome, or acute leukemia. These malignant mastocytosis does not usually involve the skin. The progression of the disease depends generally on the type of associated hematological disorder that conditions the prognosis.

The category III is represented by aggressive systemic mastocytosis in which massive infiltration of multiple organs by abnormal mast cells is common. In patients who pursue this kind of aggressive clinical course, peripheral blood features suggestive of a myeloproliferative disorder are more prominent. The progression of the disease can be very rapid, similar to acute leukemia, or some patients can show a longer survival time.

Finally, the category IV of mastocytosis includes the mast cell leukemia, characterized by the presence of circulating mast cells and mast cell progenitors representing more than 10% of the white blood cells. This entity represents probably the rarest type of leukemia in humans, and has a very poor

prognosis, similar to the rapidly progressing variant of malignant mastocytosis. Mast cell leukemia can occur either de novo or as the terminal phase of urticaria pigmentosa or systemic mastocytosis.

The invention also contemplates the method as depicted for the treatment of recurrent bacterial infections, resurging infections after asymptomatic periods such as bacterial cystitis. More particularly, the invention can be practiced for treating FimH expressing bacteria infections such as Gram-negative enterobacteria including *E. coli*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Citrobacter freundii* and *Salmonella typhimurium*. In this method for treating bacterial infection, separate, sequential or concomitant administration of at least one antibiotic selected bacitracin, the cephalosporins, the penicillins, the aminoglycosides, the tetracyclines, the streptomycins and the macrolide antibiotics such as erythromycin; the fluoroquinolones, actinomycin, the sulfonamides and trimethoprim, is of interest.

In one preferred embodiment, the invention is directed to a method for treating neoplastic diseases such as mastocytosis, canine mastocytoma, human gastrointestinal stromal tumor ("GIST"), small cell lung cancer, non-small cell lung cancer, acute myelocytic leukemia, acute lymphocytic leukemia, myelodysplastic syndrome, chronic myelogenous leukemia, colorectal carcinomas, gastric carcinomas, gastrointestinal stromal tumors, testicular cancers, glioblastomas, and astrocytomas comprising administering a compound as defined herein to a human or mammal, especially dogs and cats, in need of such treatment.

In one other preferred embodiment, the invention is directed to a method for treating allergic diseases such as asthma, allergic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, angioedema, atopic dermatitis, allergic contact dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing vasculitis and insect bite skin inflammation and blood sucking parasitic infestation comprising administering a compound as defined herein to a human or mammal, especially dogs and cats, in need of such treatment.

In still another preferred embodiment, the invention is directed to a method for treating inflammatory diseases such as rheumatoid arthritis, conjunctivitis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions comprising administering a compound as defined herein to a human in need of such treatment.

In still another preferred embodiment, the invention is directed to a method for treating autoimmune diseases such as multiple sclerosis, psoriasis, intestine inflammatory disease, ulcerative colitis, Crohn's disease, rheumatoid arthritis and polyarthritis, local and systemic scleroderma, systemic lupus erythematosus, discoid lupus erythematosus, cutaneous lupus, dermatomyositis, polymyositis, Sjogren's syndrome, nodular panarteritis, autoimmune enteropathy, as well as proliferative glomerulonephritis comprising administering a compound as defined herein to a human in need of such treatment.

In still another preferred embodiment, the invention is directed to a method for treating graft-versus-host disease or graft rejection in any organ transplantation including kidney, pancreas, liver, heart, lung, and bone marrow comprising administering a compound as defined herein to a human in need of such treatment.

## In Vitro TK Inhibition Assays

## Procedure

Experiments were performed using purified intracellular domain of c-kit expressed in baculovirus. Estimation of the kinase activity was assessed by the phosphorylation of tyrosine containing target peptide estimated by established ELISA assay.

## Experimental Results on Tested Compounds

Result in Table 1 shows the potent inhibitory action of the catalytic activity of c-kit with an  $IC_{50} < 10 \mu M$ . Further experiments (not shown) indicates that at least one compound acts as perfect competitive inhibitors of ATP.

TABLE 1

Compounds	In vitro Inhibition assay results c-kit $IC_{50}$ ( $\mu M$ )
066; 074; 078; 084; 012; 016; 073; 021; 088; 023; 025; 047; 048; 055; 049; 026; 087; 075; 089; 051; 082; 090; 060; 085; 052; 053; 096	<10 $\mu M$

## Example 2

## Ex Vivo TK Inhibition Assays

## Procedures

## C-Kit WT and Mutated C-Kit (JM) Assay

## Proliferation Assays

Cells were washed two times in PBS before plating at  $5 \times 10^4$  cells per well of 96-well plates in triplicate and stimulated either with hematopoietic growth factors (HGF) or without. After 2 days of culture, 37 Bq (1.78 Tbq/mmol) of [ $^3H$ ] thymidine (Amersham Life Science, UK) was added for 6 hours. Cells were harvested and filtered through glass fiber filters and [ $^3H$ ] thymidine incorporation was measured in a scintillation counter. For proliferation assay, all drugs were prepared as 20 mM stock solutions in DMSO and conserved at  $-80^\circ C$ . Fresh dilutions in PBS were made before each experiment. DMSO dissolved drugs were added at the beginning of the culture. Control cultures were done with corresponding DMSO dilutions. Results are represented in percentage by taking the proliferation without inhibitor as 100%.

## Cells

Ba/F3 murine kit and human kit, Ba/F3 mkit $\Delta 27$  (juxtamembrane deletion) are derived from the murine IL-3 dependent Ba/F3 proB lymphoid cells. The FMA3 and P815 cell lines are mastocytoma cells expressing endogenous mutated forms of Kit, i.e., frame deletion in the murine juxtamembrane coding region of the receptor-codons 573 to 579. The human leukaemic MC line HMC-1 expresses mutations JM-V560G;

## Immunoprecipitation Assays and Western Blotting Analysis

For each assay,  $5 \times 10^6$  Ba/F3 cells and Ba/F3-derived cells with various c-kit mutations were lysed and immunoprecipitated as described (Beslu et al., 1996), excepted that cells were stimulated with 250 ng/ml of rmKL. Cell lysates were immunoprecipitated with a rabbit immunoserum anti murine KIT, directed against the KIT cytoplasmic domain (Rottapel

67

et al., 1991). Western blot was hybridized either with the 4G10 anti-phosphotyrosine antibody (UBI) or with the rabbit immunoserum anti-murine KIT or with different antibodies (described in antibodies paragraph). The membrane was then incubated either with HRP-conjugated goat anti mouse IgG antibody or with HRP-conjugated goat anti rabbit IgG antibody (Immunotech). Proteins of interest were then visualized by incubation with ECL reagent (Amersham).

#### Experimental Results

The experimental results for various compounds according to the invention using above-described protocols are set forth at Table 2:

TABLE 2

Target	IC50 ( $\mu$ M)	Compounds
c-Kit WT	IC50 <10 $\mu$ M	002; 005; 006; 007; 008; 009; 010; 012; 017; 019; 020; 045; 047; 048; 049; 050; 051; 052; 053; 054; 055; 056; 057; 059; 060; 061; 062; 063; 064; 065; 066; 067; 072; 073; 074; 075; 077; 078; 079; 080; 081; 082; 083; 084; 085; 086; 087; 088; 089; 090; 092; 093; 094; 095; 096; 097; 106; 105; 104; 103; 128; 129; 130; 131; 117; 110; 116; 124; 108; 122; 111; 113; 118; 107;
c-Kit JM A27	IC50 <1 $\mu$ M	028; 074; 029; 009; 012; 073; 020; 042; 061; 065; 088; 025; 048; 049; 050; 089; 051; 082; 090; 083; 059; 052; 053; 066; 103; 067; 104; 078; 079; 105; 081; 084; 030; 010; 021; 043; 054; 062; 106; 023; 024; 064; 047; 055; 026; 087; 075; 085; 005; 077; 092; 060; 032; 017; 063; 093; 094; 095; 086; 093; 096; 108; 117; 122; 008; 080; 111; 118; 113; 007; 072; 019; 056; 057; 107; 097;

#### Example 3

##### In Vivo Activity

##### Procedures

##### GIST

cells: Ba/F3 cells were transfected by c-kit gene having A27 mutation (GIST model). Ba/F3 expressing the mutated c-kit gene readily proliferate in the absence of IL3 or SCF and are tumorigenic in nude mice.

##### Protocol:

Mice were irradiated at J-1 (5Gy)

Tumor cells ( $10^6$ ) were subcutaneously grafted at J0

Tumor size were daily measured from J14

Number of survival mice were daily estimated

In this experimental model, the tumor size at J14 is about 20 mm<sup>3</sup>

Treated mice received per os twice a day a dose of 100 mg/kg of one compound of formula II-3 during 5 days (from J26 to J30).

##### Rheumatoid Arthritis

The mice were pretreated with the compound of formula II-3 (2x, 12.5 mg/kg) for two days (day-2, day-1) before induction of arthritis. Arthritis was induced by ip injection of 150- $\mu$ l serums at days 0 and 2. The treatment with the compound (2x, 12.5 mg/kg) was continued for 14 days. The control mice were injected with, 1% PBS before the induction of arthritis and during the course of the disease. Ankle thickness and arthritis score was evaluated for 15 days. Arthritis Score: 5  $\mu$ m of scores of each limb (0 no disease; 1 mild swelling of paw or of just a few digits; 2 clear joint inflammation; 3 severe joint inflammation) maximum score=12. Table 3A and Table 3B show the number of mice used in this

68

study. Two sets of experiments were done with different number of mice, one with 4 mice the other with 8 mice.

TABLE 3A

Treated Mice 2x, 12.5 mg/Kg	C57B1/6 6
--------------------------------	--------------

TABLE 3B

Controls 2X, 1% PBS	C57B1/6 6
------------------------	--------------

##### Histology

At the end of the experiment the hind limbs were collected. The skin of the limb was removed and the limbs were subsequently fixed in 2% Para formaldehyde.

##### Experimental Results

##### GIST

Treated mice (with one compound of formula II-3) displays significant decrease of tumor size at J30 and J33 compared to control.

##### When administrated per os, one tested compound of the formula II-3 displays a significant antitumor activity against tumors cells expressing c-kit A27.

##### RA

A compound of the formula II-3 has demonstrated significant activity in the in vivo mouse model of arthritis. Results are shown on FIGS. 1, 2, 3, 4.

#### BRIEF DESCRIPTION OF DRAWINGS

FIG. 1: Effect of the compound in serum transfer experiments, Protocol, ip daily treatment with the compound (2x12.5 mg/kg) and on days-2 and -1, set of experiment with 4 mice (T: treated, C: control)

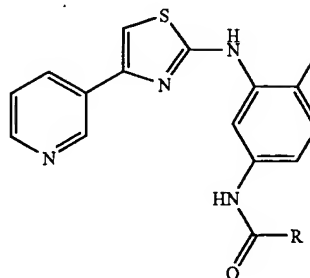
FIG. 2: Effect of the compound in serum transfer experiments, Protocol, ip daily treatment with the compound (2x12.5 mg/kg) and on days-2 and -1, set of experiment with 4 mice (T: treated, C: control)

FIG. 3: Effect of the compound in serum transfer experiments, Protocol, ip daily treatment with the compound (2x12.5 mg/kg) and on days -2 and -1, set of experiment with 8 mice (T: treated, C: control)

FIG. 4: Effect of the compound in serum transfer experiments, Protocol, ip daily treatment with the compound (2x12.5 mg/kg) and on days-2 and -1, set of experiment with 8 mice (T: treated, C: control)

The invention claimed is:

1. A compound according to the following formula:

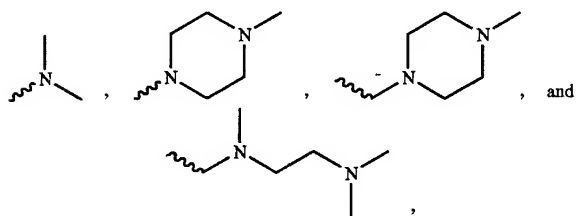


69

wherein R is:

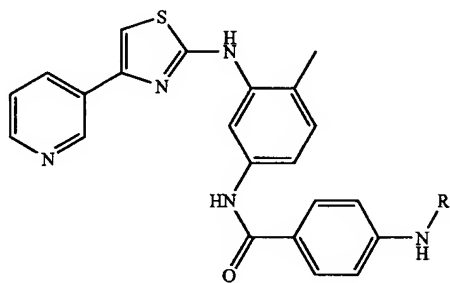
H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a

pendant basic nitrogen functionality is selected from the group consisting of



wherein the wavy line corresponds to the point of attachment.

2. A compound according to the following formula:



wherein R is:

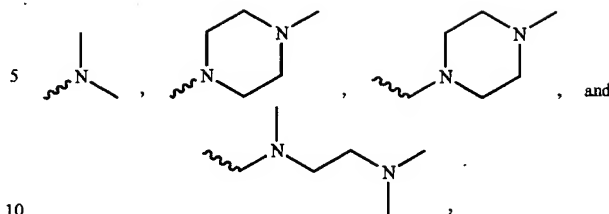
H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one substituent selected from I, Cl, Br, F, and a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one substituent selected from I, Cl, Br, F, and a pendant basic nitrogen functionality; or

a  $\text{—SO}_2\text{—R''}$  group wherein R'' is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality; or

a  $\text{—CO—R'}$  or  $\text{—CO—NR'R''}$  group, wherein R' and R'' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

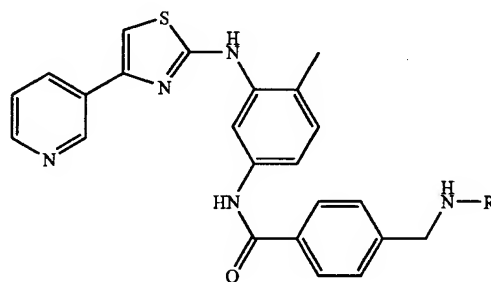
wherein said pendant basic nitrogen functionality is selected from the group consisting of

70



wherein the wavy line corresponds to the point of attachment.

3. A compound according to the following formula:



wherein R is H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

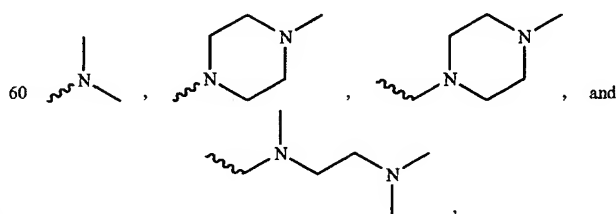
a cycloalkyl, aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

an alkyl, cycloalkyl, aryl or heteroaryl group substituted by a alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

a  $\text{—SO}_2\text{—R''}$  group wherein R'' is an alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

a  $\text{—CO—R'}$  or a  $\text{—CO—NR'R''}$  group, wherein R' and R'' are independently chosen from H or an aryl heteroaryl, alkyl and cycloalkyl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

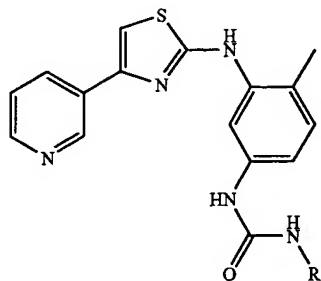
wherein said pendant basic nitrogen functionality is selected from the group consisting of



wherein the wavy line corresponds to the point of attachment.

71

4. A compound according to of the following formula:



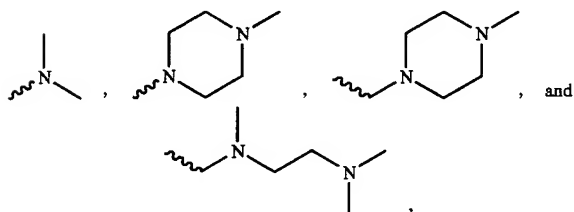
wherein R is:

H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality; or

a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality; or

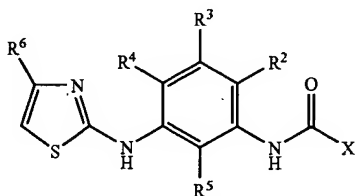
a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

wherein said pendant basic nitrogen functionality is selected from the group consisting of



wherein the wavy line corresponds to the point of attachment.

5. A compound according to formula II:



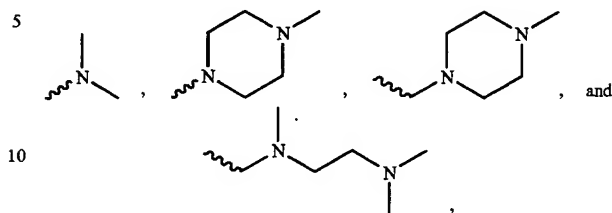
FORMULA II

wherein X is R or NRR' and wherein R and R' are independently chosen from H, an aryl, an heteroaryl, an alkyl and a cycloalkyl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

an aryl, an heteroaryl, an alkyl and a cycloalkyl group substituted with an aryl, an heteroaryl, an alkyl and a cycloalkyl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

72

wherein said pendant basic nitrogen functionality is selected from the group consisting of



wherein the wavy line corresponds to the point of attachment;

R<sup>2</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>3</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>4</sup> is halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>5</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>6</sup> is one of the following:

(i) an aryl group optionally substituted by one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, or alkoxy;

(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear one or more substituents;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl, which may additionally bear one or more substituents.

6. A compound according to claim 5 selected from the group consisting of:

1-(4-Bromo-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 010);

1-(4-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 012);

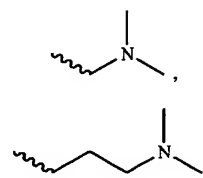
1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-thiophen-2-yl-urea (example 015);

1-(3,5-Dimethyl-isoxazol-4-yl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 019);

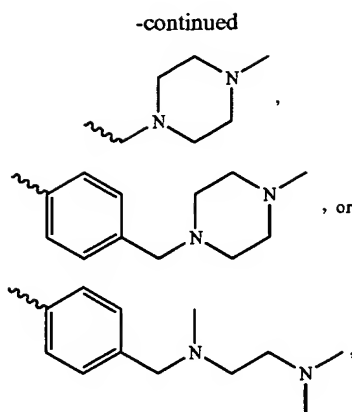
1-(2-Iodo-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 020); and

1-(4-Dimethylamino-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 022).

7. A compound according to claim 5, wherein X is selected from the structures (a)-(d) and (f) shown below:



73



wherein the wavy line corresponds to the point of attachment to core structure of formula II.

8. A compound according to claim 7, wherein X is group (d) and R<sup>6</sup> is a 3-pyridyl group.

9. A compound according to claim 7, wherein X is group (d) and R<sup>4</sup> is a methyl group.

10. A compound according to claim 7, wherein X is group (d) and R<sup>2</sup> and/or R<sup>3</sup> and/or R<sup>5</sup> is H.

11. The compound of claim 5 which is: 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-4-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 080).

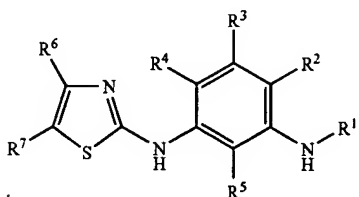
12. A compound which is: N-{3-[4-(4-cyano-phenyl)-thiazol-2-ylamino]}-4-methyl-phenyl)-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 081).

13. The compound of claim 5 which is: 4-(4-methyl-piperazin-1-yl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 060) or 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 066).

14. A compound which is: 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 066).

15. A composition comprising a compound of claim 14 and a pharmaceutically acceptable carrier.

16. A compound of formula I:



wherein R<sup>1</sup> is:

—C(O)R, —C(O)OR, or —CO—NRR', wherein R and R' are independently selected from the group consisting of hydrogen, aryl, heteroaryl, alkyl, and cycloalkyl, each optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality;

R<sup>2</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

74

R<sup>3</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>4</sup> is halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>5</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>6</sup> is one of the following:

(i) an aryl group such as phenyl optionally substituted by one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, or alkoxy;

(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear one or more substituents; or

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl, which may additionally bear one or more substituents;

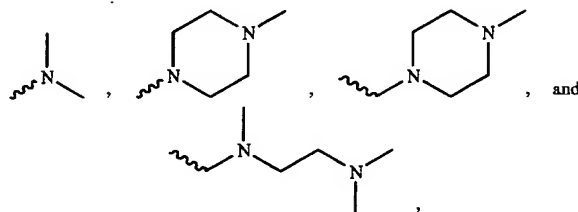
and R<sup>7</sup> is one of the following:

(i) an aryl group such as phenyl optionally substituted by one or more substituents;

(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear one or more substituents;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl, which may additionally bear one or more substituents; or

(iv) H, a halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> and SO<sub>2</sub>—R", wherein R" is a linear or branched alkyl group optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality; wherein said pendant basic nitrogen functionality is selected from the group consisting of



FORMULA I

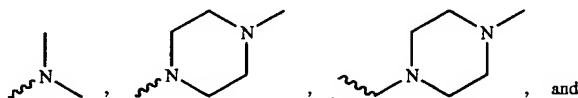
wherein the wavy line corresponds to the point of attachment.

17. A composition comprising a compound of claim 16 in a pharmaceutically acceptable carrier.

18. A compound according to claim 16, wherein R' is

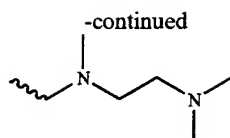
—C(O)R, wherein R is independently selected from the group consisting of hydrogen, aryl, heteroaryl, alkyl, and cycloalkyl, each optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality;

wherein said pendant basic nitrogen functionality is selected from the group consisting of





75



wherein the wavy line corresponds to the point of attachment.

19. A compound according to claim 18 selected from the group consisting of:

N-[4-Methyl-3-(4-phenyl-thiazol-2-ylamino)-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 004);

N-[3-([2,4']Bithiazolyl-2'-ylamino)-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide; (example 005);

N-[4-Chloro-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 027);

3-Bromo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 028);

3-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 029);

2-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 032);

4-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 033);

3-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 045);

4-Dimethylamino-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 047);

4-(4-Methyl-piperazin-1-yl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-benzamide (example 060);

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-isonicotinamide (example 063);

2,6-Dichloro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-isonicotinamide (example 064);

3,5-Dibromo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 067);

3-Fluoro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 074);

2,3,5,6-Tetrafluoro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 076);

N-[3-[4-(4-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 077);

3-Bromo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 078);

3-Chloro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 079);

N-[4-Methyl-3-[4-(5-methyl-pyridin-3-yl)-thiazol-2-ylamino]-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 084);

3-Iodo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 085);

3-Dimethylamino-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 088);

76

3-(4-Methyl-piperazin-1-yl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 089);

Cyclohexanecarboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide (example 092);

5-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-pentanoic acid ethyl ester (example 093);

4-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 104);

N-[3-[4-(4-Chloro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 108);

N-[3-[4-(4-Methoxy-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 110);

N-[3-[4-(3-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 111);

N-[3-[4-(3-Methoxy-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 113);

4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-[4-(3-trifluoromethyl-phenyl)-thiazol-2-ylamino]-phenyl]-benzamide (example 116);

N-[3-[4-(2-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 118);

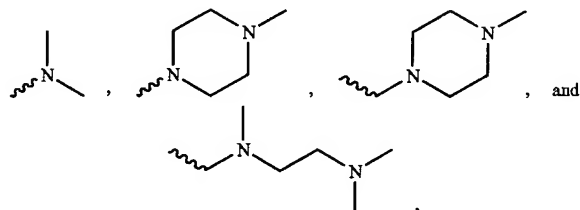
4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-2-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 122); and

N-[3-[4-(2,5-Dimethyl-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 124).

20. A pharmaceutical composition comprising a compound according to claim 18 and a pharmaceutically acceptable carrier.

21. A compound according to claim 16, wherein R' is —CO—NRR', wherein R and R' are independently selected from the group consisting of hydrogen, aryl, heteroaryl, alkyl, and cycloalkyl, each optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality;

wherein said pendant basic nitrogen functionality is selected from the group consisting of



wherein the wavy line corresponds to the point of attachment.

22. A compound according to claim 21 selected from the group consisting of:

1-(2-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 023);

1-(2-Chloro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 024); and

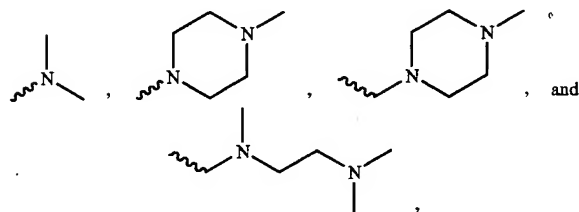
1-(3-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 025).



77

23. A pharmaceutical composition comprising a compound according to claim 21 and a pharmaceutically acceptable carrier.

24. A compound according to claim 16, wherein R' is —C(O)OR, wherein R is selected from the group consisting of hydrogen, aryl, heteroaryl, alkyl, and cycloalkyl, each optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality; wherein said pendant basic nitrogen functionality is selected from the group consisting of



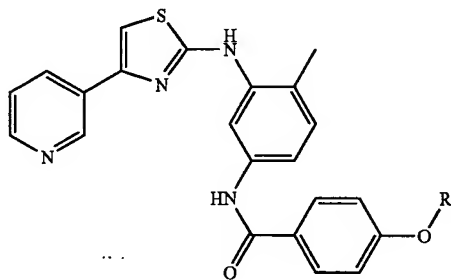
wherein the wavy line corresponds to the point of attachment.

25. A compound according to claim 24 selected from the group consisting of:

[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-carbamic acid isobutyl ester (example 097), and [4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-carbamic acid tert-butyl ester (example 098).

26. A pharmaceutical composition comprising a compound according to claim 25 and a pharmaceutically acceptable carrier.

27. A compound according to the following formula:



wherein R is H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom, or bearing at least one pendant basic nitrogen functionality;

a cycloalkyl, aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality; or

an alkyl, cycloalkyl, aryl or heteroaryl group substituted by a alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality; or

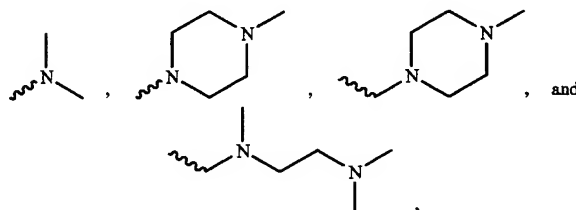
a —SO<sub>2</sub>-R'' group wherein R'' is an alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

a —CO—R' or a —CO—NR'R''—group wherein R' and R'' are independently chosen from H or an aryl het-

78

eroaryl, alkyl and cycloalkyl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

wherein said pendant basic nitrogen functionality is selected from the group consisting of selected from the group consisting of



wherein the wavy line corresponds to the point of attachment.

28. A compound according to claim 27 selected from the group consisting of

4-Hydroxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 037);

Thiophene-2-sulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester (example 042);

4-Iodo-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester (example 043);

4-Isopropoxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 050);

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(2-morpholin-4-yl-ethoxy)-benzamide (example 052);

3-Fluoro-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester (example 056);

2-Fluoro-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester (example 058); and

3-Methoxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 059).

29. A compound according to claim 2 selected from the group consisting of

4-[3-(4-Bromo-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 036);

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-(3-thiophen-2-yl-ureido)-benzamide (example 038);

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-(thiophene-2-sulfonylamino)-benzamide (example 044);

4-[3-(2-Iodo-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 101); and

4-[3-(4-Fluoro-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 102).

30. A compound selected from the group consisting of 1-(4-Methoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 009);

1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(4-trifluoromethyl-phenyl)-urea (example 011);

1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(3,4,5-trimethoxy-phenyl)-urea (example 013);

4-{3-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-ureido}-benzoic acid ethyl ester (example 014);  
 1-Cyclohexyl-1-(N-Cyclohexyl-formamide)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 016);  
 1-(2,4-Dimethoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 017);  
 1-(2-Iodo-phenyl)-1-(N-(2-Iodo-phenyl)-formamide)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 018);  
 1-(4-Difluoromethoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 021);  
 1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-p-tolyl-urea (example 026);  
 (4-Hydroxymethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 030);  
 4-(3-{4-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]carbamoyl}-phenyl)-ureido)-benzoic acid ethyl ester (example 034);  
 N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide (example 035);  
 4-[3-(3,5-Dimethyl-isoxazol-4-yl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 039);  
 4-[3-(4-Methoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 040);  
 4-[3-(4-Difluoromethoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 041);  
 2-Fluoro-5-methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 048);  
 4-tert-Butyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 049);

Benzo [1,3]dioxole-5-carboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide (example 051);  
 3-Cyano-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 054);  
 2-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide (example 055);  
 3-Methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 061);  
 Biphenyl-3-carboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide (example 062);  
 N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide (example 065);  
 {4-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]carbamoyl}-benzyl]-carbamic acid tert-butyl ester (example 073);  
 3-Fluoro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 074);  
 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide (example 075);  
 4-(1-Methoxy-ethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 083);  
 N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[3-(4-trifluoromethyl-phenyl)-ureidomethyl]-benzamide (example 086);  
 4-Cyano-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 103);  
 4-[3-(2,4-Dimethoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 100); and  
 3-Bromo-4-methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 105).

\* \* \* \* \*

## EXHIBIT B

FORM PTO-1595 (modified)

(Rev 6-93)

REC

01-14-2004



102645416

U.S. DEPARTMENT OF COMMERCE

HEET

Patent and Trademark Office

To the Director of the United States Patent and Trademark Office.

Attached original documents or copies thereof.

## 1. Name of conveying party(ies):

Marco Ciufolini  
Camille Georges Wermuth  
Bruno Marie Gielthen  
Alain Moussy

## 2. Name and address of receiving party(ies):

AB Science  
3, Avenue Georges V  
Paris  
75008  
France

2001 JAN 12 AM 8:57  
OPR/FINANCE

Additional conveying party(ies)

NO

## 3. Nature of conveyance:

ASSIGNMENTS

Execution Dates:

10/29/03

Additional name(s) &amp; address(es) attached?

NO

## 4. Application number(s) or patent number(s):

If this is being filed together with a new application, the execution date of the application is:

A. Patent Application Number(s):

10/632,101

B. Patent Number(s):

PATENT\_NO

Additional numbers attached? NO

## 5. Name and address of party to whom correspondence concerning document should be mailed:

David P. Lentini  
FOLEY & LARDNER  
One Maritime Plaza  
Sixth Floor  
San Francisco, California 94111-3404

## 6. Total number of applications/patents involved: 1

## 7. Total fee (37 C.F.R. § 3.41): \$40.00

☒ Check Enclosed

Charge to deposit account

## 8. Deposit account number: 19-0741

DO NOT USE THIS SPACE

## 9. Statement and signature:

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document. The Commissioner is hereby authorized to charge any additional recordation fees which may be required in this matter to the above-identified deposit account.

David P. Lentini

1/8/04

Name of person signing

Signature

Date

Total number of pages including cover sheet, attachments, and document: 7

01/13/2004 DBYRHE 00000064 10632101

01 FC:8021

40.00 OP

016.319569.1

PATENT

REEL: 014872 FRAME: 0028

**ASSIGNMENT**

*For good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, each undersigned inventor has sold and assigned, and by these presents hereby sells and assigns, unto*

name and **AB SCIENCE**  
address of **3, Avenue Georges V**  
assignee **Paris, France 75008**

*(hereinafter ASSIGNEE) all right, title and interest for the United States, its territories and possessions in and to this invention relating to*

*title of invention*  
**2-(3-aminoaryl)amino-4-aryl-thiazoles for the treatment of diseases**  
*as set forth in this United States Patent Application*

check one ☐ executed concurrently herewith  
☐ executed on  
☒ Serial No. 10/632,101 Filed AUGUST 1, 2003

*in and to said United States Patent Application including any and all divisions or continuations thereof and in and to any and all Letters Patent of the United States which may issue on any such application or for said invention, including any and all reissues or extensions thereof, to be held and enjoyed by said ASSIGNEE, its successors, legal representatives and assigns to the full end of the term or terms for which any and all such Letters Patent may be granted as fully and entirely as would have been held and enjoyed by the undersigned had this Assignment not been made;*

*Each of the undersigned hereby authorizes and requests the Commissioner of Patents and Trademarks to issue any and all such Letters Patent to said ASSIGNEE, its successors or assigns in accordance herewith;*

*Each of the undersigned warrants and covenants that he has the full and unencumbered right to sell and assign the interests herein sold and assigned and that he has not executed and will not execute any document or instrument in conflict herewith;*

*Each of the undersigned further covenants and agrees he will communicate to said ASSIGNEE, its successors, legal representatives or assigns all information known to him relating to said invention or patent application and that he will execute and deliver any papers, make all rightful oaths, testify in any legal proceedings and perform all other lawful acts deemed necessary or desirable by said ASSIGNEE, its successors, legal representatives or assigns to perfect title to said invention, in said application including divisions and continuations thereof and to any and all Letters Patent which may be granted therefor or thereon, including reissues or extensions, in said ASSIGNEE, its successors, or assigns or to assist said ASSIGNEE, its successors, legal representatives or assigns in obtaining, reissuing or enforcing Letters Patent of the United States for said invention;*

*Each of the undersigned hereby assigns all right title and interest to this invention to said ASSIGNEE for patent applications in any country claiming benefit of the priority of the present United States application.*


-1-

**PATENT**

**REEL: 014872 FRAME: 0029**

# ASSIGNMENT

Each of the undersigned hereby authorizes the firm of **FOLEY & LARDNER** to insert in this Assignment any further identification which may be necessary or desirable to comply with the rules of the U.S. Patent and Trademark Office for recordation of this Assignment.

<b>NAMES AND SIGNATURES OF INVENTORS</b>		
Name: <b>Marco CIUFOLINI</b>	Signature:	Date:
Name: <b>Camille WERMUTH</b>	Signature:	Date:
Name: <b>Bruno GIELTHEN</b>	Signature:	Date:
Name: <b>Alain MOUSSY</b>	Signature 	Date: <b>10/29/03</b>
<b>NAMES AND SIGNATURES OF WITNESSES</b>		
Name:	Signature:	Date:
Name:	Signature:	Date:
Name:	Signature:	Date:
Name:	Signature:	Date:

Note: Prima facie evidence of execution may optionally be obtained by execution of this document before a U.S. Consul or before a local officer authorized to administer oaths whose authority is proved by a certificate from a U.S. Consul.

**ASSIGNMENT**

*For good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, each undersigned inventor has sold and assigned, and by these presents hereby sells and assigns, unto*

name and **AB SCIENCE**  
 address of **3, Avenue Georges V**  
 assignee **Paris, France 75008**

*(hereinafter ASSIGNEE) all right, title and interest for the United States, its territories and possessions in and to this invention relating to*

*title of invention*  
**2-(3-aminoaryl)amino-4-aryl-thiazoles for the treatment of diseases**  
*as set forth in this United States Patent Application*

check one ☐ *executed concurrently herewith*  
☐ *executed on*  
☒ *Serial No.* **10/632,101** *Filed* **AUGUST 1, 2003**

*in and to said United States Patent Application including any and all divisions or continuations thereof and in and to any and all Letters Patent of the United States which may issue on any such application or for said invention, including any and all reissues or extensions thereof, to be held and enjoyed by said ASSIGNEE, its successors, legal representatives and assigns to the full end of the term or terms for which any and all such Letters Patent may be granted as fully and entirely as would have been held and enjoyed by the undersigned had this Assignment not been made;*

*Each of the undersigned hereby authorizes and requests the Commissioner of Patents and Trademarks to issue any and all such Letters Patent to said ASSIGNEE, its successors or assigns in accordance herewith;*

*Each of the undersigned warrants and covenants that he has the full and unencumbered right to sell and assign the interests herein sold and assigned and that he has not executed and will not execute any document or instrument in conflict herewith;*

*Each of the undersigned further covenants and agrees he will communicate to said ASSIGNEE, its successors, legal representatives or assigns all information known to him relating to said invention or patent application and that he will execute and deliver any papers, make all rightful oaths, testify in any legal proceedings and perform all other lawful acts deemed necessary or desirable by said ASSIGNEE, its successors, legal representatives or assigns to perfect title to said invention, to said application including divisions and continuations thereof and to any and all Letters Patent which may be granted therefor or thereon, including reissues or extensions, in said ASSIGNEE, its successors, or assigns or to assist said ASSIGNEE, its successors, legal representatives or assigns in obtaining, reissuing or enforcing Letters Patent of the United States for said invention;*

*Each of the undersigned hereby assigns all right title and interest to this invention to said ASSIGNEE for patent applications in any country claiming benefit of the priority of the present United States application.*

# ASSIGNMENT

Each of the undersigned hereby authorizes the firm of **FOLEY & LARDNER** to insert in this Assignment any further identification which may be necessary or desirable to comply with the rules of the U.S. Patent and Trademark Office for recordation of this Assignment.

NAMES AND SIGNATURES OF INVENTORS		
Name: Marco CIUFOLINI	Signature:	Date:
Name: Camille WERMUTH	Signature: C.G.W. - <i>[Signature]</i>	Date: 10/29/03
Name: Bruno GIELTHEN	Signature: <i>[Signature]</i>	Date: 10/29/03
Name: Alain MOUSSY	Signature	Date:
NAMES AND SIGNATURES OF WITNESSES		
Name:	Signature:	Date:
Name:	Signature:	Date:
Name:	Signature:	Date:
Name:	Signature:	Date:

Note: Prima facie evidence of execution may optionally be obtained by execution of this document before a U.S. Consul or before a local officer authorized to administer oaths whose authority is proved by a certificate from a U.S. Consul.



**ASSIGNMENT**

*For good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, each undersigned inventor has sold and assigned, and by these presents hereby sells and assigns, unto*

name and      **AB SCIENCE**  
 address of    **3, Avenue Georges V**  
 assignee      **Paris, France 75008**

*(hereinafter ASSIGNEE) all right, title and interest for the United States, its territories and possessions in and to this invention relating to*

*title of invention*  
**2-(3-aminoaryl)amino-4-aryl-thiazoles for the treatment of diseases**  
*as set forth in this United States Patent Application*

check one      ☐ *executed concurrently herewith*  
                   ☐ *executed on* \_\_\_\_\_  
                   ☒ *Serial No.* 10/632,101      *Filed* AUGUST 1, 2003

*in and to said United States Patent Application including any and all divisions or continuations thereof and in and to any and all Letters Patent of the United States which may issue on any such application or for said invention, including any and all reissues or extensions thereof, to be held and enjoyed by said ASSIGNEE, its successors, legal representatives and assigns to the full end of the term or terms for which any and all such Letters Patent may be granted as fully and entirely as would have been held and enjoyed by the undersigned had this Assignment not been made;*

*Each of the undersigned hereby authorizes and requests the Commissioner of Patents and Trademarks to issue any and all such Letters Patent to said ASSIGNEE, its successors or assigns in accordance herewith;*

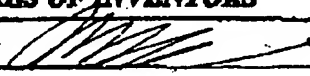
*Each of the undersigned warrants and covenants that he has the full and unencumbered right to sell and assign the interests herein sold and assigned and that he has not executed and will not execute any document or instrument in conflict herewith;*

*Each of the undersigned further covenants and agrees he will communicate to said ASSIGNEE, its successors, legal representatives or assigns all information known to him relating to said invention or patent application and that he will execute and deliver any papers, make all rightful oaths, testify in any legal proceedings and perform all other lawful acts deemed necessary or desirable by said ASSIGNEE, its successors, legal representatives or assigns to perfect title to said invention, to said application including divisions and continuations thereof and to any and all Letters Patent which may be granted therefor or thereon, including reissues or extensions, in said ASSIGNEE, its successors, or assigns or to assist said ASSIGNEE, its successors, legal representatives or assigns in obtaining, reissuing or enforcing Letters Patent of the United States for said invention;*

*Each of the undersigned hereby assigns all right title and interest to this invention to said ASSIGNEE for patent applications in any country claiming benefit of the priority of the present United States application.*

# ASSIGNMENT

Each of the undersigned hereby authorizes the firm of **FOLEY & LARDNER** to insert in this Assignment any further identification which may be necessary or desirable to comply with the rules of the U.S. Patent and Trademark Office for recordation of this Assignment.

NAMES AND SIGNATURES OF INVENTORS		
Name: Marco CIUFOLINI	Signature: 	Date: 1-1-23/2003
Name: Camille WERMUTH	Signature:	Date:
Name: Bruno GIELTHEN	Signature:	Date:
Name: Alain MOUSSY	Signature:	Date:
NAMES AND SIGNATURES OF WITNESSES		
Name:	Signature:	Date:
Name:	Signature:	Date:
Name:	Signature:	Date:
Name:	Signature:	Date:

Note: Prima facie evidence of execution may optionally be obtained by execution of this document before a U.S. Consul or before a local officer authorized to administer oaths whose authority is proved by a certificate from a U.S. Consul.

## EXHIBIT C

**KINAVET-CA1**  
(masitinib mesylate)  
Tablet  
Antineoplastic

For oral use in dogs only

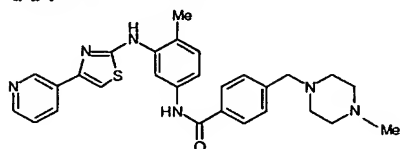
**Conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-308.**

**CAUTION:**

Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Use only as directed. It is a violation of Federal law to use this product other than as directed in the labeling.

**DESCRIPTION:**

Masitinib is a tyrosine kinase inhibitor. The molecular weight of masitinib base is 498.67. The empirical formula is  $C_{26}H_{30}N_6O_5S$ . The structural formula is:



KINAVET-CA1 tablets are round, biconvex, orange, coated tablets, containing either 50 mg or 150 mg masitinib base as masitinib mesylate. Each tablet is engraved with logo on one side and dosage strength on the other side.

**INDICATIONS:**

KINAVET-CA1 tablets are indicated for the treatment of recurrent (post-surgery) or nonresectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and/or chemotherapy except corticosteroids.

**DOSAGE AND ADMINISTRATION:**

*Always provide Client Information Sheet with prescription.*

Administer KINAVET-CA1 at an initial dose of 12.5 mg/kg/day (5.7 mg/lb/day) orally, once daily with food (see Table 1). Dose reductions to 9 mg/kg/day (4.1 mg/lb/day, see Table 2) and dose interruptions may be utilized, if needed, to manage adverse reactions (see Table 3 as well as **WARNINGS** and **PRECAUTIONS**). Do not split or crush tablets.

Table 1. Initial Dose, 12.5 mg/kg/day Dose Chart

Dog Body Weight		Dose	Number of Tablets	
Pounds	Kilograms		50 mg	150 mg
15.4 - 22.9	7.0 - 10.4	100 mg	2	
23.0 - 30.6	10.5 - 13.9	150 mg		1
30.7 - 39.4	14.0 - 17.9	200 mg	1	1
39.5 - 48.2	18.0 - 21.9	250 mg	2	1
48.3 - 57.0	22.0 - 25.9	300 mg		2
57.1 - 65.8	26.0 - 29.9	350 mg	1	2
65.9 - 74.6	30.0 - 33.9	400 mg	2	2
74.7 - 83.4	34.0 - 37.9	450 mg		3
83.5 - 92.2	38.0 - 41.9	500 mg	1	3
92.3 - 101.0	42.0 - 45.9	550 mg	2	3
101.1 - 110.2	46.0 - 49.9	600 mg		4
110.3 - 118.6	50.0 - 53.9	650 mg	1	4
118.7 - 127.4	54.0 - 57.9	700 mg	2	4
127.5 - 136.2	58.0 - 61.9	750 mg		5
136.3 - 145.0	62.0 - 65.9	800 mg	1	5
145.1 - 153.8	66.0 - 69.9	850 mg	2	5
153.9 - 162.6	70.0 - 73.9	900 mg		6
162.7 - 171.4	74.0 - 77.9	950 mg	1	6
171.5 - 220	78.0 - 100.0	1000 mg	2	6

\*KINAVET-CA1 cannot be safely dosed at the target dose of 12.5 mg/kg in dogs weighing less than 7.0 kg (15.4 lbs)

Table 2. Reduced Dose, 9 mg/kg/day Dose Chart

Dog Body Weight		Dose	Number of Tablets	
Pounds	Kilograms		50 mg	150 mg
15.4 - 22.9	7.0 - 10.4	Discontinue treatment*		
23.0 - 31.7	10.5 - 14.4	100 mg	2	
31.8 - 42.7	14.5 - 19.4	150 mg		1
42.8 - 54.8	19.5 - 24.9	200 mg	1	1
54.9 - 67.1	25.0 - 30.5	250 mg	2	1
67.2 - 79.4	30.6 - 36.1	300 mg		2
79.5 - 91.5	36.2 - 41.6	350 mg	1	2
91.6 - 103.8	41.7 - 47.2	400 mg	2	2
103.9 - 115.9	47.3 - 52.7	450 mg		3
116.0 - 128.3	52.8 - 58.3	500 mg	1	3
128.4 - 140.4	58.4 - 63.8	550 mg	2	3
140.5 - 152.7	64.0 - 69.4	600 mg		4
152.8 - 164.8	69.5 - 74.9	650 mg	1	4
164.9 - 177.1	75.0 - 80.5	700 mg	2	4
177.1 - 220	80.6 - 100.0	750 mg		5

\*KINAVET-CA1 cannot be effectively dosed at 9 mg/kg in dogs weighing less than 10.5 kg (23.0 lbs)

Table 3. Managing Adverse Reactions with Dose Interruption or Reduction

Toxicity	Dose Adjustment
<b>Renal Toxicities and Protein Loss Syndrome</b>	
Hypoalbuminemia (serum albumin < 0.75X LLN*) Proteinuria (UPC > 1) Azotemia (BUN or Creatinine > 1.5X ULN*)	If the current dose is 12.5 mg/kg, discontinue treatment until resolution, then resume treatment at 9 mg/kg. If the current dose is 9 mg/kg then permanently discontinue treatment.
<b>Non-Regenerative Anemia and Hemolytic Anemia</b>	
Hematocrit < 30% Hemoglobin < 10 g/dL	Permanently discontinue treatment.
<b>Neutropenia</b>	
Neutrophils < 1500/ $\mu$ L	If the current dose is 12.5 mg/kg, discontinue treatment until resolution, then resume treatment at 9 mg/kg. If the current dose is 9 mg/kg, permanently discontinue treatment.
<b>Hepatic Toxicity</b>	
ALT or AST > 3X ULN Bilirubin > 1.5X ULN	If the current dose is 12.5 mg/kg, discontinue treatment until resolution, then resume treatment at 9 mg/kg. If the current dose is 9 mg/kg, permanently discontinue treatment.
<b>Gastrointestinal Toxicity</b>	
Vomiting and Diarrhea Grade 3 or greater*	If the current dose is 12.5 mg/kg, discontinue treatment until resolution, then resume treatment at 9 mg/kg. If the current dose is 9 mg/kg, permanently discontinue treatment.
<b>Other Adverse Reactions</b>	
Severe Weight Loss	Permanently discontinue treatment.

\*LLN = lower limit of normal

†ULN = upper limit of normal

\*Grade 3 diarrhea is an increase of > 6 stools per day over baseline. Grade 3 vomiting is > 5 vomiting episodes in 24 hours, or vomiting for > 4 days.†

**CONTRAINDICATIONS:**

Do not initiate KINAVET-CA1 tablet treatment in dogs with:

- Hypoalbuminemia (serum albumin < 1X LLN)
- Proteinuria (urine protein to creatinine [UPC] ratio > 1)
- Azotemia (elevated blood urea nitrogen or creatinine > 1 ULN)
- Anemia (hematocrit < 30 % or hemoglobin < 10 g/dL)
- Neutropenia (< 2000/ $\mu$ L)
- AST or ALT elevations (> 3X ULN)
- Hyperbilirubinemia (> 1.5X ULN)

Do not use in dogs that are pregnant, lactating, or intended for breeding. Masitinib caused impaired fertility, fetal resorptions and abnormal development (delayed ossification) in rats.

Do not use in dogs that have a hypersensitivity to masitinib.

**WARNINGS:**

Masitinib was associated with life-threatening or fatal hypoalbuminemia and anemia in field studies and the 39-week safety study. The studies provide evidence that severe adverse reactions may be prevented if dogs are monitored for hypoalbuminemia every 2 weeks and for anemia every 4 weeks, and treatment is discontinued if hypoalbuminemia, proteinuria or anemia occur (see Table 3 and **ANIMAL SAFETY**).

**HUMAN WARNINGS:**

**NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.** Children should not come into contact with KINAVET-CA1. Keep children away from feces, urine, or vomit of treated dogs.

To avoid exposure to drug, wash hands with soap and water after administering KINAVET-CA1 and wear protective gloves to prevent contact with feces, urine, vomit, and broken or crushed KINAVET-CA1 tablets. Place all waste material in a plastic bag and seal before general disposal. If eyes are accidentally exposed to the drug, rinse eyes with water immediately. In case of accidental ingestion by a person, seek medical advice immediately, show the package insert or label to the physician.

Pregnant women, women who may become pregnant, or nursing mothers should pay special attention to these handling precautions (see handling instructions above). KINAVET-CA1 may harm an unborn baby (cause birth defects). For pregnant and nursing women, accidental ingestion of KINAVET-CA1 may have adverse effects on pregnancy or the nursing baby.

## PRECAUTIONS:

Dogs on KINAVET-CA1 tablets should be monitored as follows:

<b>Every 2 weeks:</b>	Hypoalbuminemia Proteinuria
<b>Every 4 weeks:</b>	Azotemia Anemia Neutropenia Elevated AST or ALT Hyperbilirubinemia

In case of a positive semi-quantitative test for proteinuria (dipstick protein  $\geq 30$  mg/dL) or clinical signs of anemia or hemolysis, urine protein should be confirmed with a quantitative test (UPC ratio) and the dog should be tested for hypoalbuminemia, anemia, and azotemia.

Refer to Table 3 under DOSAGE AND ADMINISTRATION for management of adverse reactions.

The safe use of KINAVET-CA1 tablets has not been evaluated in dogs younger than 2 years of age. KINAVET-CA1 cannot be safely dosed in dogs weighing less than 7 kg (15.4 lbs).

KINAVET-CA1 is metabolized in the liver. The influence of concomitant drugs that may inhibit metabolism of KINAVET-CA1 tablets has not been evaluated in dogs. Drug compatibility should be assessed for dogs requiring concomitant therapy. Concomitant treatment with drugs which are metabolized by CYP450 isoenzymes (3A4, 3A5, 2C9, 2D6) may result in higher or lower plasma levels of either KINAVET-CA1 or those drugs, and should be used with caution (see CLINICAL PHARMACOLOGY).

The concomitant use of potentially nephrotoxic drugs and KINAVET-CA1 has not been evaluated.

Vascular homeostasis in dogs taking KINAVET-CA1 that require surgery has not been evaluated.

## ADVERSE REACTIONS:

Adverse reactions associated with KINAVET-CA1 treatment include:

<b>General:</b>	lethargy, weakness, dehydration, behavioral changes, death
<b>Gastrointestinal:</b>	vomiting, diarrhea, bloody stools, melena, constipation, decreased appetite, anorexia
<b>Renal:</b>	azotemia, proteinuria, elevated UPC, polyuria, polydipsia, hemoglobinuria, hematuria, nephrotic/protein loss syndrome
<b>Hepatic:</b>	elevated liver enzymes, elevated bilirubin, ascites, icterus
<b>Cardiorespiratory:</b>	cough, pleural effusion, possible pulmonary thromboembolism, dyspnea, hypertension, tachycardia, cardiomegaly, syncope, circulatory collapse, aspiration pneumonia
<b>Metabolic:</b>	pancreatitis, weight loss, tumor lysis syndrome, mast cell degranulation, periodic hypoglycemia
<b>Hematologic:</b>	anemia, hemolytic anemia, non-regenerative anemia, leukopenia, neutropenia, lymphopenia, thrombocytopenia
<b>Ocular:</b>	hyphema
<b>Skin:</b>	alopecia, increased incidence of lipomas, subcutaneous edema, pruritis
<b>Other:</b>	lymphadenopathy, hemoabdomen, back pain

Refer to Table 3, under DOSAGE AND ADMINISTRATION for management of adverse reactions.

For a copy of the Material Safety Data Sheet (MSDS) or to report adverse reactions, contact AB Science, USA at 973-218-2436 or contact@ab-science.com.

## INFORMATION FOR DOG OWNER:

The dog owner or person responsible for administering KINAVET-CA1 to the dog should receive and read the Client Information Sheet, which describes how to safely administer KINAVET-CA1, monitor for possible adverse reactions and clean up any urine, feces or vomit from dogs treated with KINAVET-CA1. The Client Information Sheet also contains warnings for humans and what to do in case of accidental human exposure to KINAVET-CA1.

## CLINICAL PHARMACOLOGY:

Masitinib is a protein-tyrosine kinase inhibitor. Protein tyrosine kinases are thought to be activated in cancer cells and to drive tumor progression. Tyrosine kinase inhibitor drugs act by interfering with these cell communications and may prevent tumor growth. *In vitro*, masitinib selectively inhibits the mutated form of the c-Kit receptor (a receptor tyrosine kinase) in the juxtamembrane region and the c-Kit wild-type receptor. It also inhibits the platelet-derived growth factor receptor and the fibroblast growth factor receptor 3.

Following oral administration of  $11.2 \pm 0.5$  mg/kg masitinib, as KINAVET-CA1 tablets, in dogs, masitinib was rapidly absorbed reaching a mean ( $\pm$  1SD) peak plasma concentration of  $895 (\pm 283)$  ng/mL at  $2.29 (\pm 0.83)$  hours. The mean area under the plasma concentration time-curve (AUC 0-24) was  $5.70 (\pm 1.93)$   $\mu\text{g} \times \text{hr/mL}$ . The mean elimination half-life ( $t_{1/2}$ ) is  $3.24 (\pm 0.42)$  hours. Following administration of KINAVET-CA1 tablets, the fed  $C_{max}$  was 136% (90% Confidence Limits: 98 – 190%) and the fed AUC was 114% (52 – 252%) of the fasted  $C_{max}$  and AUC, respectively.

The plasma total body clearance and volume of distribution of masitinib in normal healthy Beagle dogs is approximately 14 mL/min/kg and 17 L/kg, respectively. Masitinib is approximately 90% bound to plasma proteins. Minimal accumulation occurs when masitinib is administered daily at a dose of 12.5 mg/kg. Based on masitinib plasma concentrations at clinically relevant doses in toxicity studies, the inter-animal coefficient of variation in AUC (representing bioavailability) is expected to be about 25%.

Masitinib is metabolized predominantly by N-dealkylation. Elimination is principally in the bile and gastrointestinal tract. *In vitro* testing with human liver microsomes demonstrated that masitinib inhibits the activity of cytochrome P450 isozymes CYP2C9, 2D6, 3A4 and 3A5. Results of *in vitro* testing with human hepatocytes were inconsistent; therefore, the potential for masitinib to induce the activity of cytochrome P450 isozymes is unclear.

## EFFECTIVENESS:

### Reasonable Expectation of Effectiveness

Effectiveness has not been demonstrated for KINAVET-CA1. A reasonable expectation of effectiveness for conditional approval was based on time to progression (TTP) in a subpopulation of dogs in the following study.

A randomized, placebo controlled, double masked, multi-center field study was conducted to evaluate the safety and effectiveness of KINAVET-CA1 in dogs with Grade II or III cutaneous mast cell tumors recurrent after surgery or nonresectable without regional lymph node involvement. Two hundred and two dogs of various breeds, were enrolled, 161 received KINAVET-CA1 at a starting dose of 12.5 mg/kg orally and 41 received placebo, daily for 6 months, or until disease progression or withdrawal from the study for another cause.

The primary variable, objective response rate after 4 months of treatment, confirmed after 6 months of treatment, failed to show a statistically significant difference between the KINAVET-CA1 and placebo treated dogs: 16.1% of dogs administered KINAVET-CA1 had a complete or partial response compared to 14.6% of dogs administered placebo.

The primary variable failed. However, one of the secondary variables, TTP, in a subpopulation of dogs that did not receive previous chemotherapy and/or radiotherapy except corticosteroids, demonstrated a reasonable expectation of effectiveness. One hundred and thirteen dogs treated with KINAVET-CA1 had an increase in median TTP of 52.5 days compared to 30 dogs treated with placebo ( $p$ -value=0.0143). The median TTP in the KINAVET-CA1 group was 118 days, 80% longer than the placebo group with a median time to progression of 65.5 days. The study was not designed for TTP to support substantial evidence of effectiveness.

## ANIMAL SAFETY:

The margin of safety and toxicity profile of masitinib (not commercial formulation) was evaluated in three laboratory safety studies (for 4, 13, and 39 weeks) in healthy 6 to 7 month old Beagle dogs. Masitinib has a narrow margin of safety, and one death occurred after 33 weeks of treatment with 20.9 mg/kg/day, a dose comparable to 1.4X the maximum KINAVET-CA1 label dose of 15.0 mg/kg/day. (See Safety Study Results, below. See Table 3, WARNINGS and PRECAUTIONS for risk management.) The results of the safety studies provide the following toxicity profile for masitinib: bone marrow suppression (anemia, neutropenia, and bone marrow hypocellularity), evidence of red blood cell sequestration (splenic hemosiderosis), proteinuria and hypoalbuminemia without kidney lesions on histopathology, liver abnormalities (mildly increased liver enzymes, histopathologic lesions), gastrointestinal signs, and increased coagulation values. The 13-week safety study provides evidence that these adverse effects are reversible.

Safety Studies Results: There were no signs of toxicity at 2.1 mg/kg (0.14X) for 39 weeks or 3.5 mg/kg (0.23X) for 13 weeks.

In the 4, 13, and 39-week studies at 7.0 mg/kg (0.5X) and 10.5 mg/kg (0.7X), clinical signs included transient and infrequent vomiting, soft feces, lethargy, and muscle weakness; erythema of the neck or muzzle, pallor, mild anemia, and mild proteinuria. After 39 weeks at 7.0 mg/kg (0.5X), histopathology findings included splenic hemosiderosis, brownish pigment deposits in hepatic Kupffer cells and lymph nodes, and increased lipid tissue in the bone marrow.

In the 39-week study at 20.9 mg/kg (1.4X), a female developed severe hypoalbuminemia and proteinuria, and moderate anemia, by week 25. She was euthanized in week 33 because of ascites, emaciated appearance, decreased appetite, lateral recumbency, pallor, and severe anemia, hypoalbuminemia, hypoproteinemia, and proteinuria. She had thrombocytosis, hematuria, lymphopenia, and increased activated partial thromboplastin time (APTT), fibrinogen, and blood urea nitrogen. Necropsy and histopathology findings included pericardial, subcutaneous, and tissue edema, and severe lymphoid depletion of the thymus. Other dogs on 20.9 mg/kg (1.4X) masitinib had vomiting, lethargy, pallor, erythema of the neck, hind leg stiffness, mild anemia, neutropenia, hypoalbuminemia, and proteinuria. Histopathology findings were similar to those at 7.0 mg/kg (0.5X), but more pronounced.

In the 4 and 13-week studies at 35.1 mg/kg (2.3X), clinical signs included vomiting, diarrhea, pallor, and lethargy. Clinical pathology findings included anemia, neutropenia, decreased eosinophils, and mild hypoalbuminemia, and mild increases in APTT, fibrinogen, and liver enzymes (alanine aminotransferase and alkaline phosphatase). Histopathology findings included slight hepatocellular hypertrophy, bile canalicular plugs, vacuolated and brownish pigment-laden Kupffer cells in the liver, cystic epithelial hyperplasia of the gall bladder, foamy macrophages in the mesenteric lymph node, chronic interstitial pneumonitis, acute esophagitis, increased lipid tissue in the bone marrow, and bone marrow hypocellularity.

After 13 weeks of treatment, a subset of dogs from the 35.1 mg/kg (2.3X) treatment group were given a 4-week treatment-free recovery period. At the end of this period, the recovery dogs did not have the adverse clinical pathology and histopathology findings that were observed in dogs at the end of the 13 weeks of treatment.

In the 4-week study at 105.5 mg/kg (7.0X), clinical signs, clinical pathology, and histopathology results were similar but more severe than at 35.1 mg/kg (2.3X), and also included blood-tinged feces, decreased appetite, increased heart rate, weight loss, proteinuria, hematuria, hepatomegaly, vacuolated hepatocytes, a markedly increased myeloid to erythroid ratio, lymphoid depletion of the thymus, histiocytosis in the spleen, and foamy alveolar macrophages in the lungs.

## STORAGE CONDITIONS:

Keep at controlled room temperature (15-25°C; 59-77°F), in the original packaging, away from a source of heat or humidity.

## HOW SUPPLIED:

KINAVET-CA1 is supplied in white high density polyethylene (HDPE) bottles containing 30 tablets of 50mg masitinib base or 150mg masitinib base.

## REFERENCES:

1. Veterinary co-operative oncology group – common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy in dogs and cats v1.0. *Vet Comp Oncol* 2004;2(4):195-213.

Manufactured by:  
Catalent Pharma Solutions  
Somerset, NJ 08873  
USA

Manufactured for:  
AB Science  
3, Avenue George V  
75008 – PARIS (France)

Client	AB Science
Contact	Cyrille Denariez


Dossier	
Produit	7531
Réf	Kinavet™ CA1
	V01
Dimensions	210x297 mm
	19/11/2010

ALIAS

BAT : date et signature

Client	AB Science
Contact	Cyrille Denariez

Dossier	7535
Produit	Kinavet™ CA1
Réf	Etui 150 mg - US - <b>V1</b>
	1 langue
Dimensions	45 x 45 x 85 mm
	19/11/2010

 <p><b>KINAVET-CA1</b> <b>masitinib mesylate</b> Tablet Antineoplastic <b>150 mg</b></p> <p>30 coated tablets</p> <p>Conditionally approved by FDA pending a full demonstration of effective- ness under application number 141-308</p>	<p><b>KINAVET-CA1 150 mg</b></p> <p>For oral use in dogs only</p> <p><b>INDICATION</b> For the treatment of recurrent (post surgery) or non resectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and / or chemotherapy except corticosteroids.</p> <p><b>CAUTION</b> Federal law restricts this drug to use by or on order of a licensed veterinarian. Use only as directed. It is a violation of Federal law to use this product other than as directed in the labeling.</p> <p>See enclosed package insert for dosing information and important human safety information. Wear gloves when handling this drug.</p> <p>Manufactured by: Catalent Pharma Solutions 14 Schoolhouse Road Somerset NJ 08873 USA For: AB Science 3 avenue George V F-75008 Paris</p>	<p><b>HUMAN WARNINGS</b> NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN. Children should not come into contact with KINAVET-CA1. Keep children away from feces, urine and vomit of treated dogs. To avoid exposure to drug, wash hands with soap and water after administering KINAVET-CA1 and wear protective gloves to prevent contact with feces urine, vomit, and broken or crushed KINAVET-CA1 tablets. Place all waste material in plastic bag and seal before general disposal. If eyes are accidentally exposed to the drug, rinse eyes with water immediately. In case of accidental ingestion by a person, seek medical advice immediately, show the package insert or label to the physician. Pregnant women, women who may become pregnant, or nursing mothers should pay special attention to these handling precautions as KINAVET-CA1 belongs to a class of agents that may cause harm to the unborn baby. Keep at controlled room temperature below 25°C (&lt;77°F) in the original packaging away from a source of heat or humidity.</p>	<p>Lot: EXP:</p> <p><b>CONTRAINDICATIONS:</b> Do not initiate KINAVET-CA1 tablets treatment in dogs with proteinuria (a urine protein to creatinine (UPC) ratio &gt; 1), hypoalbuminemia (serum albumin &lt;1 time the lower limit of normal (1xULN)), elevated blood urea nitrogen or creatinine (&gt;1 time the upper normal limit (1xULN)), anemia (hematocrit&lt;30% or hemoglobin&lt;10g/dl), neutropenia (&lt;2000 mm<sup>3</sup>), hyperbilirubinemia (&gt;1.5 times the upper normal limit (1.5xULN), or ASAT/ALT &gt;3 times the upper limit of normal (3xULN)).</p> <p>Do not use in dogs that are pregnant, lactating or intended for breeding. KINAVET-CA1 caused impaired fertility, fetal resorptions and abnormal development (delayed ossification) in rats.</p> <p>Do not use in dogs that have demonstrated hypersensitivity to masitinib.</p>
<p>AB Science, 3 avenue George V F-75008 Paris</p> <p><b>KINAVET-CA1</b> <b>masitinib mesylate</b> Tablet <b>Antineoplastic</b> <b>150 mg</b></p>			
<p>7535 - V1</p> <p><b>ALIAS</b></p> <p><b>BAT : date et signature</b></p>			

Client	AB Science
Contact	Cyrille Denariez

Dossier	7533
Produit	Kinavet™ CA
Réf	Etiquette 150 mg 1 langue - US - V1
Dimensions	110 x 45 mm
	19/11/2010

*ALIAS*

BAT : date et signature

For oral use in dogs only.

CAUTION: Federal law restricts this drug to use by or on order of a licensed veterinarian. Use only as directed. It is a violation of Federal law to use this product other than as directed in the labeling.

See enclosed package insert for dosing information and important human safety information. Wear gloves when handling this drug.

Manufactured by: Catalyst Pharma Solutions  
14 Schoonhouse Road Somerset NJ 08873 USA  
For AB Science 3 Avenue George V F-75008 Paris



**KINAVET-CA1**  
masitinib mesylate  
Tablet

Antineoplastic  
**150 mg**

30 coated tablets

Conditionally approved by FDA  
pending a full demonstration of  
effectiveness under application  
number 141-308

HUMAN WARNINGS:  
NOT FOR USE IN HUMANS. KEEP THIS  
AND ALL MEDICATION OUT OF THE REACH  
OF CHILDREN.  
Keep at controlled room temperature below  
25°C (77°F) in the original packaging away  
from a source of heat or humidity.

Lot:

EXP:

www.kinavet.com

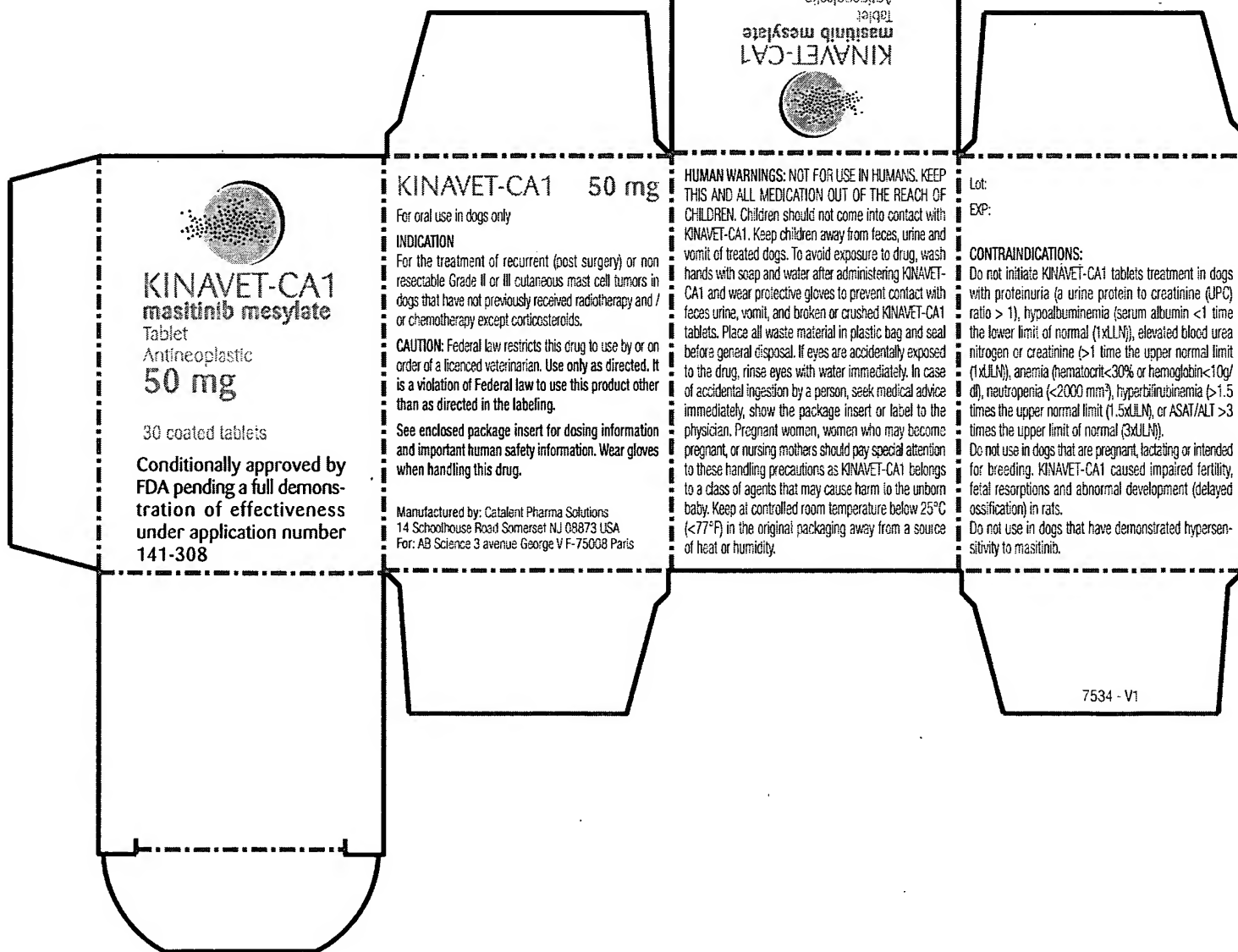
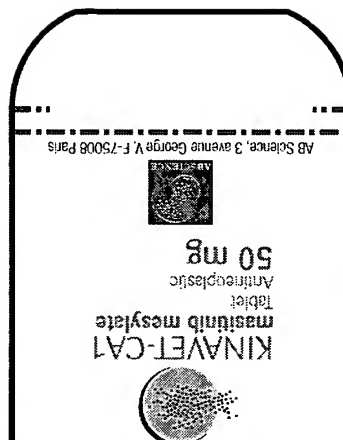


Client	AB Science
Contact	Cyrille Denariez

Dossier	7534
Produit	Kinavet™ CA1
Réf	Etui 50 mg - US - V1
	1 langue
Dimensions	45 x 45 x 65 mm
	19/11/2010

*ALIAS*

BAT : date et signature



7534 - V1

Cliant	AB Science
Contact	Cyrille Denariez

Dossier	7532
Produit	Kinavet™ CA1
Réf	Etiquette 50 mg 1 langue US - V1
Dimensions	110 x 28 mm
	19/11/2010

BAT : date et signature

*ALIAS*

306 coated tablets. For oral use in dogs only.  
CAUTION: Federal law restricts this drug to use by or on order of a licensed veterinarian. Use only as directed. It is a violation of Federal law to use this product other than as directed in the labeling. See enclosed package insert for dosing information and important human safety information. Wear gloves when handling this drug.

Manufactured by: Culler Pharma Solutions  
14 Colchester Road Somerset TA5 8JY U.K.A.  
For AS Science 3 Animal George F 7-2008 7416



**KINAVET-CA1**  
masitinib mesylate  
Tablet  
50 mg

Conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-308

HUMAN WARNINGS: NOT FOR USE IN HUMANS. KEEP THIS AND ALL INFORMATION OUT OF THE REACH OF CHILDREN. Keep at controlled room temperature below 25°C (77°F) in the original packaging away from a source of heat or humidity.

Lot:  
Exp:

www.kinavet.com

## EXHIBIT D

**Application No. 141-308-A-0000-OT**  
**CONDITIONAL APPROVAL DATE: December 15, 2010**  
**CVM#201083**



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR VETERINARY MEDICINE**

**FACSIMILE TRANSMISSION**

DATE: December 15, 2010	TIME: 4:00 p.m.
TO: The Anson Group Attention: Michael R. Langley DVM, MBA, RAC US Agent on behalf of AB Science 11460 North Meridian Street Carmel, IN 46032	FROM: <input type="checkbox"/> Dr. Mary Allen <input type="checkbox"/> Dr. Mohammad Sharar <input type="checkbox"/> Ms. Bonnie Bodo <input checked="" type="checkbox"/> Dr. Robin Keyser OFFICE OF NEW ANIMAL DRUG EVALUATION HFV-107
TEL. 317-569-9500 Ext.103	DHHS/FDA/CVM/ONADE/HFV-107 TEL. <input type="checkbox"/> (240) 276-8128 <input type="checkbox"/> (240) 276-9179 <input type="checkbox"/> (240) 276-8198 <input checked="" type="checkbox"/> (240) 276-8130
FAX: 317-569-9520	METRO PARK NORTH II 7500 STANDISH PLACE ROCKVILLE, MD 20855

Number of pages (including cover sheet): 3

CVM/ONADE FAX NUMBER: (240) 276-8242



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Food and Drug Administration  
Rockville MD 20857

DEC 15 2010

Application Number 141308-A-0000-OT

The Anson Group  
Attention: Michael R. Langley DVM, MBA, RAC  
US Agent on behalf of AB Science  
11460 North Meridian Street  
Carmel, IN 46032

Re: Request for conditional approval of KINAVET-CA1

Dear Dr. Langley:

We conditionally approve your conditional approval application for one year for KINAVET-CA1 dated July 9, 2010, amended July 22, 2010 (M-0001), September 2, 2010 (M-0002), and September 16, 2010 (M-0003), under section 571(b) of the Federal Food, Drug, and Cosmetic Act (the act). KINAVET-CA1 (masitinib mesylate) Tablets is conditionally approved for the treatment of recurrent (post-surgery) or nonresectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and/or chemotherapy except corticosteroids in dogs. We forwarded a notice of this conditional approval for publication in the FEDERAL REGISTER. You must notify us of any change to the conditions established in this conditional approval according to 21 CFR 514.8. In addition, you must comply with the records and reporting requirements concerning post-approval experience with this conditionally approved new animal drug according to 21 CFR 514.80. If you fail to make the required reports or maintain the required records under 21 CFR 514.80, your conditional approval would be subject to the withdrawal provisions of section 571(e)(3) of the act.

This application for conditional approval is conditionally approved for one year from the date of this letter. This application is renewable annually for up to four additional one-year terms. A request to renew this application must be submitted no later than 90 days from the end of the one-year period starting on the date of this letter. This request must include sufficient information to show that you are making sufficient progress toward meeting the approval requirements under section 512(d)(1)(E) of Federal Food, Drug, and Cosmetic Act (the act), that the quantity of the drug distributed is consistent with the conditionally approved intended use and conditions of use, and the same drug in the same dosage form for the same intended use has not received approval under Section 512.

KINAVET-CA1 in the dosage form and the intended uses conditionally approved by FDA under application number 141-308 qualifies for seven years of exclusive marketing rights beginning as of the date of this conditional approval letter. Your new animal drug qualifies

Application Number 141308-A-0000-OT

Page 2

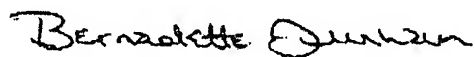
for exclusive marketing rights under section 573(c) of the Federal Food, Drug, and Cosmetic Act (the act) because it has been declared a designated new animal drug by FDA under section 573(a) of the act. Any remaining portion of the exclusive marketing period will apply to a fully approved product if there is no lapse in the conditional approval status and full approval is obtained within five years of this conditional approval.

Your final printed labeling must be identical to the approved facsimile labeling submitted September 16, 2010 (N-141308-M-0003) except change the Caution statement on the package insert, carton and bottle label, from "*Extra-label use of this drug is prohibited by Federal law.*" to "*It is a violation of Federal law to use this product other than as directed in the labeling.*" Please submit in triplicate three paper copies (a total of nine copies) of each component of the final printed labeling before distributing and marketing your new animal drug.

The expiration dating for this new animal drug is 24 months. Under current good manufacturing practice (cGMP) regulations (21 CFR 211 and 226), you are required to validate your manufacturing processes. This validation provides assurance that the manufacturing processes will reliably meet predetermined specifications. This validation is demonstrated by documenting that the manufacturing processes are adequate to preserve the identity, strength, quality, and purity of the new animal drug. If your validation information was not available or was found deficient at the time of the pre-approval inspection, you should contact FDA after you complete manufacturing validation and before you ship the product. A product that does not conform to cGMP is adulterated under section 501(a) of the act.

If you submit correspondence relating to this conditional approval, your correspondence should reference the date and the principal submission identifier found at the top of this letter. If you have any questions or comments, contact Dr. Mary E. Allen, Acting Director, Division of Therapeutic Drugs for Non-Food Animals, at 240-276-8337.

Sincerely,



Bernadette M. Dunham, D.V.M., Ph.D.

Director

Center for Veterinary Medicine

Enclosure:

Freedom of Information Summary

## EXHIBIT E

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING  
REJECTION OVER A PENDING "REFERENCE" APPLICATION**

Docket Number (Optional)  
065691-0332

In re Application of: Marco Ciufolini et al.

Application No.: 10/632,101

Filed: August 1, 2003

For: 2-(3-aminoaryl)amino-4-aryl-thiazoles for the Treatment of Diseases

The owner\*, AB Science, 3 av George V, Paris, France, of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number 11/779,633, filed on July 18, 2007, as such term is defined in 35 U.S.C. 154 and 173, and as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

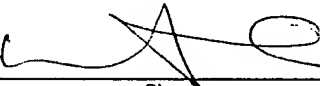
In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that: any such patent: granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 39,221

  
\_\_\_\_\_  
Signature  
\_\_\_\_\_  
Rouget F. Henschel  
Typed or printed name  
\_\_\_\_\_  
April 10, 2008  
Date  
\_\_\_\_\_  
(202) 295-4059  
Telephone Number

- ☒ Terminal disclaimer fee under 37 CFR 1.20(d) is included.

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

\*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).  
Form PTO/SB/96 may be used for making this statement. See MPEP § 324.

This collection of information is required by 37 CFR 1.321. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.



## EXHIBIT G

Date of Approval: DEC 15 2010

# FREEDOM OF INFORMATION SUMMARY

## APPLICATION FOR CONDITIONAL APPROVAL

Application 141-308

KINAVET-CA1

Masitinib mesylate

Tablet

Dog

For the treatment of recurrent (post-surgery) or nonresectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and/or chemotherapy except corticosteroids

Sponsored by:

AB Science

Paris, France

## TABLE OF CONTENTS

I.	GENERAL INFORMATION:	1
II.	EFFECTIVENESS:	2
	A. Dosage Characterization:	2
	B. Reasonable Expectation of Effectiveness:	3
III.	TARGET ANIMAL SAFETY:	5
	A. Relative Bioavailability (Bridging) Study	5
	B. 4-Week Toxicity Study	7
	C. 13-Week Toxicity Study	14
	D. 39-Week Toxicity Study	19
IV.	HUMAN FOOD SAFETY:	25
V.	USER SAFETY:	25
VI.	AGENCY CONCLUSIONS:	26
	A. Marketing Status:	26
	B. Exclusivity:	26
	C. Patent Information:	26
VII.	ATTACHMENTS:	27

**I. GENERAL INFORMATION:**

**A. Application Number:** 141-308

**B. Sponsor:** AB Science  
3 Avenue George V  
75008 Paris, France

Drug Labeler Code: 052913

US Agent:  
Michael R. Langley, DVM, MBA, RAC  
The Anson Group  
11460 North Meridian Street  
Carmel, Indiana USA 46032

**C. Proprietary Name(s):** KINAVET-CA1

**D. Established Name(s):** Masitinib mesylate

**E. Pharmacological Category:** Anti-neoplastic

**F. Dosage Form(s):** Tablet

**G. Amount of Active Ingredient(s):** 50 mg or 150 mg

**H. How Supplied:** KINAVET-CA1 tablets are available as round biconvex orange coated tablets. Each tablet is engraved with the logo on one side and the mg strength on the other side. The tablets are packaged in 30-count bottles.

**I. How Dispensed:** Rx

**J. Dosage(s):** 12.5 mg/kg/day (5.7 mg/lb/day)

**K. Route(s) of Administration:** Oral

**L. Species/Class(es):** Dog

**M. Indication(s):** For the treatment of recurrent (post-surgery) or nonresectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and/or chemotherapy except corticosteroids.

## II. EFFECTIVENESS:

The active ingredient in KINAVET-CA1 is referred to as masitinib or AB1010 and the two names are used interchangeably.

**Conditional Dose:** The conditional dose for the indication “for the treatment of recurrent (post-surgery) or nonresectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and/or chemotherapy except corticosteroids” is 12.5 mg/kg/day (5.7 mg/lb/day). The safety data and reasonable expectation of effectiveness data presented in this document and the data to demonstrate a reasonable expectation of effectiveness provide support for this conditional use.

### A. Dosage Characterization:

Three toxicity studies were conducted for target animal safety and were used to help identify a conditional dose in dogs. The conditional dose of 12.5 mg/kg/day was chosen based upon the maximum tolerated dose. See TARGET ANIMAL SAFETY for more information.

In the uncontrolled field study AB03099 titled “Efficacy and Safety of AB1010 in the Treatment of Canine Mast Cell Tumors” conducted in 13 dogs with Grade II or III mast cell tumors, 10 dogs received masitinib mesylate at a dose of 12.5 mg/kg once daily, 2 dogs received 15 mg/kg twice daily and 1 dog received 4.4 mg/kg once daily. The study assessed the effectiveness and safety of masitinib mesylate on canine mast cell tumors based on objective response rate (complete and partial response) over a 12-week period. The objective tumor response was defined as the ratio of current tumor volume to baseline tumor volume and expressed as a percentage:  $\text{tumor response} = 100 \times (\text{current volume}/\text{baseline volume})$ . Complete response was defined as a tumor response equal to 0%. Partial response was defined as a tumor response  $\leq 50\%$ , with no increase in size of a previously documented lesion or development of new lesions. Four dogs were removed from analysis; 1 dog had a Grade I mast cell tumor and 3 were treated for 10 days or less. The analysis showed 2 out of 9 dogs had a complete response and 2 out of 9 had a partial response at 12 weeks. The objective response was 44% (4/9). One dog with complete response received the 4.4 mg/kg once daily dose. The other 3 dogs with objective response received the 12.5 mg/kg once daily dose. Neutropenia and vomiting were the most common adverse reactions. Edema was also seen. Two dogs were euthanized: 1 for vomiting and lethargy, and 1 for gastric ulcerations, vomiting, and increased liver values. Based on the objective response rate achieved, this study contributed to justifying 12.5 mg/kg/day as an effective dose for treatment.

Masitinib systemic bioavailability was slightly greater following co-administration with food. The effect of food on the pharmacokinetics of masitinib mesylate tablets was tested in a laboratory study of 6 male 8 month old Beagle dogs, using a crossover design and a 7-day washout period. For the fasted treatment, dogs were fasted overnight and food was given 4 hours after a dose of 11.9 mg/kg masitinib mesylate tablets. For the fed treatment, dogs were fed half of their daily ration 30 minutes before dosing and the remaining half immediately after a dose of 11.6 mg/kg masitinib mesylate tablets. The

Fed mean area under the plasma masitinib concentration time-curve (AUC) was 114% (90% Confidence Limits: 52 to 252%) of the Fasted AUC. The Fed mean peak plasma masitinib concentration ( $C_{max}$ ) was 136% (90% Confidence Limits: 98-190%) of the Fasted  $C_{max}$ , and occurred earlier. The time to peak plasma masitinib concentration ( $T_{max}$ ) occurred at 1 to 2 hours for fed versus 1 to 4 hours fasted.

**B. Reasonable Expectation of Effectiveness:**

The multi-center field study AB04003 titled "Multicentric, randomized, double-blind, placebo-controlled clinical field study to demonstrate the efficacy and safety of AB1010 in the control/treatment of Mast Cell Tumors in dogs" was evaluated to support a reasonable expectation of effectiveness for conditional approval. Two hundred and two dogs with Grade II or III mast cell tumors recurrent after surgery or nonresectable without regional lymph node or systemic involvement were enrolled. One hundred and sixty-one received KINAVET-CA1 tablets at a starting dose of 12.5 mg/kg/day and 41 received a placebo tablet. The objective was to demonstrate the effectiveness and safety of masitinib mesylate at the dose of 12.5 mg/kg/day in comparison to placebo.

Enrolled dogs had at least 1 tumor that measured a minimum of 10 mm in diameter. Dogs were excluded if they had renal insufficiency, gastrointestinal bleeding, neutropenia, elevated liver transaminases, other serious diseases, been previously treated with a tyrosine kinase inhibitor, were lactating or pregnant, intended for breeding, under 6 months of age, or weighed less than 3.3 kg.

Variables Measured

The primary evaluation of effectiveness was based on the objective response rate (complete response and partial response) after 4 months (Day 112) of treatment and confirmed after 6 months (Day 168) of treatment. See Table 1 below.

Table 1: Disease Response Definitions

Response	Definition
Complete Response (CR)	Tumor response <sup>a</sup> = 0%
Partial Response (PR)	Tumor response $\leq$ 51%, with no increase in size of previously documented area or any new lesion development.
Stable Disease (SD)	Tumor response between 51% to 124% with no increase in size of previously documented area or any new lesion development.
Progressive Disease (PD)	All other cases.

<sup>a</sup> Tumor response =  $100 \times (\text{current volume}/\text{baseline volume})$

Secondary variables evaluated during the study included time to progression (TTP), progression-free survival, overall survival, best response rate, complete response rate at each time point, overall response rate, and control disease rate. In addition, these

variables were analyzed for different sub-populations including dogs not treated previously with chemotherapy and/or radiotherapy except corticosteroids.

The dogs were examined on day 0, 7, 14, 28, 42, 56, 84, 112, 140 and 168. Tumor assessment, complete blood count (CBC), chemistry profile and urinalysis were performed at each visit. Dose interruptions and/or dose reductions to 9 mg/kg could be made at these visits if adverse reactions occurred. Minimum hematological and biochemical values required to continue treatment at 12.5 mg/kg/day or the reduced dose: neutrophil count > 1000/ $\mu$ L, hematocrit > 20%, platelet count > 100,000/ $\mu$ L, liver transaminases  $\leq$  5.0 times the upper limit normal, and creatinine < 4.0 mg/dL.

### Results

The study, designed to measure the primary variable, objective response rate, failed to show a statistically significant difference between the masitinib mesylate and placebo treated dogs. In the intent to treat population, 16.1% of the patients on masitinib mesylate responded to treatment, compared to 14.6% on placebo. When evaluating a subpopulation of no previous chemotherapy and/or radiotherapy except corticosteroids, 18.9% of the patients on masitinib mesylate responded to treatment, compared to 10.0% on placebo. The intent to treat population included all dogs enrolled in the study.

Table 2: Objective Response Rate in the Intent to Treat Population

Objective Tumor Response	Masitinib % Response	Placebo % Response	P-value <sup>a</sup>
All dogs (n = 202)	16.1	14.6	0.831
No previous chemotherapy/ radiotherapy (n = 152)	18.9	10.0	0.294

<sup>a</sup> Exact Cochran-Mantel-Haenzsel test comparing treatments, stratified on tumor grade and type

Although the primary variable failed, one of the secondary variables, time to progression, demonstrated significance in the no previous chemotherapy and/or radiotherapy except corticosteroids sub-population. The secondary variable provides the basis for reasonable expectation of effectiveness. This analysis is based on the per protocol population, which only included dogs that met the entrance criteria for the study.

Table 3: Time to Progression in the Per Protocol Population

Time to Progression	Median Masitinib (days)	Median Placebo (days)	$\Delta$ Median (days)	$\Delta$ Median (%)	P-value <sup>a</sup>
All dogs (n = 186)	112	65.5	+46.5	+71	0.1234
No previous chemotherapy/ radiotherapy (n = 143)	118	65.5	+52.5	+80	0.0143

<sup>a</sup> Log rank test comparing treatments

In the sub-population, dogs without previous chemotherapy and/or radiotherapy, the impact of masitinib mesylate on time to progression was better than in the overall population. The study was not designed for TTP to support substantial evidence of effectiveness.

#### Adverse Reactions

Adverse reactions that occurred in dogs treated with masitinib more frequently than the placebo group included vomiting, diarrhea, elevated liver enzymes, alopecia, decreased appetite, neutropenia, lethargy, cough, ocular disorders, anorexia, lymphadenopathy, subcutaneous edema, azotemia, hypoalbuminemia, hypoproteinemia, elevated urine protein creatinine ratio (UPC), proteinuria, renal failure, asthenia, lipoma, anemia, hemolytic anemia, constipation, dyspnea, circulatory collapse, dehydration, hypoglycemic seizure, pleural effusion, cardiomegaly, tachycardia, syncope, intra-abdominal hemorrhage, pancreatitis, aspiration pneumonia, back pain, spinal cord compression, inability to walk, fatigue, pruritus, behavioral changes and death.

#### Conclusion

The study results suggest there is a reasonable expectation of effectiveness for the use of KINAVET-CA1 (masitinib mesylate) tablets for the treatment of Grade II or III nonresectable or recurrent (post-surgery) cutaneous mast cell tumors in dogs not previously treated by radiotherapy and/or chemotherapy except corticosteroids.

### **III. TARGET ANIMAL SAFETY:**

#### **A. Relative Bioavailability (Bridging) Study**

- Study Title: Relative Bioavailability Study after Single Oral Administration of a Solution and Two Different Tablet Formulations to Male Beagle Dogs. Study No. 30487 PAC
- Type of Study: Laboratory study
- Study Dates: October 2005



d) Study Director and Location: Terence Appelqvist, CIT, Evreux, France

e) General Design

Purpose of Study: To compare the bioavailability of an oral solution used in the toxicity studies to the veterinary tablet.

Study Animals: Fifteen male Beagle dogs (approximately 7 months of age) were randomly allocated to three treatment groups of 5 dogs each.

Treatment Groups: Each treatment group was treated with each of the three dosage forms (solution and two different tablet forms) in a crossover design, separated by a 7-day washout period. On the three treatment days (Days 1, 8, and 15), each treatment group received a different formulation.

Drug Administration: The three dosage forms included a veterinary tablet and another tablet formulation, each containing 100 mg masitinib base, and a solution of 2.5 mg/mL masitinib base in normal saline. Over the course of the study, each dog was treated with one veterinary tablet, the other tablet, and 40 mL of solution. Tablet administration was followed with 40 mL of tap water by syringe; the solution was administered by gavage. Dogs were fasted overnight prior to each treatment, and then fed 6 hours after dosing.

Measurements and Observations: Blood samples were collected pre-dose and at 0.5, 1, 2, 3, 4, 6, 9, 12, 16, 24, and 48 hours post-dosing. The dogs were monitored for vomiting within the first hour post-dosing, mortality, clinical signs, and body weight.

Statistical Methods: Bioequivalence was assessed using 90% confidence intervals on log transformed data.

f) Results

One dog vomited after receiving the solution, and the plasma concentration data for this dog was not included in the statistical analysis. Excessive salivation was observed in this dog and in one other dog following gavage with the solution. Excessive salivation was not reported in any dogs after administration of the tablets. The results show that the bioavailability of masitinib veterinary tablets is 18% greater than the solution formulation administered by gavage. See Table 4 below.

Table 4: Pharmacokinetic Parameters Derived from Masitinib Concentrations

Parameter	Solution Mean (SD)	Veterinary Tablet Mean (SD)	90% CL <sup>a</sup>
Dose (mg/kg)	11.3 (0.5)	11.2 (0.5)	N/A
C <sub>max</sub> (ng/mL)	819 (437)	895 (283)	113 [93, 133] <sup>c</sup>
T <sub>max</sub> (hour)	1.9 (0.9)	2.3 (0.8)	N/A
AUC <sub>0-1</sub> (hr·ng/mL) <sup>b</sup>	4746 (1566)	5701 (1934)	118 [100, 137] <sup>c</sup>
Half-life (hour)	3.4 (0.3)	3.2 (0.4)	N/A
AUC <sub>0-∞</sub> (hr·ng/mL)	4790 (1586)	5758 (1969)	N/A

<sup>a</sup> CL estimated on Log Transform data. Values listed as Mean [Lower Limit, Upper Limit].

<sup>b</sup> AUC<sub>0-1</sub> values were determined by log-linear trapezoidal rule.

<sup>c</sup> Comparison: Veterinary Tablet/Solution

- g) Conclusions for the Relative Bioavailability (Bridging) Study: Masitinib veterinary tablets are 18% more bioavailable than the masitinib solution formulation administered by gavage in the toxicity studies. In the descriptions of the toxicity studies, for ease of comparison of dose group results to the label dose, this FOI Summary provides doses comparable to KINAVET-CA1 tablet doses (i.e., 18% less than the toxicity study doses of masitinib base in solution).

#### B. 4-Week Toxicity Study

- Study Title and Number: 4-Week Toxicity Study By Oral Route (Gavage) In Beagle Dogs Followed by a 2-Week Treatment-Free Period, Study No. 24371 TSC.
- Type of Study: GLP laboratory study, toxicity study with pharmacokinetics
- Study Dates: April – May 2003
- Study Director and Location: Isabelle Gaou, CIT, Evreux, France
- General Design

Purpose of Study: To evaluate the potential toxicity of an oral solution of masitinib, administered daily for 4 weeks, and the potential reversibility of findings after a subsequent 2-week treatment-free recovery period.

Study Animals: Thirty-two Beagle dogs (approximately 6 months of age) were randomly allocated to three test item groups and one control group.

Treatment Groups:

Table 5: Treatment Group Doses for the 4-Week Toxicity Study

<b>Treatment Group</b>	<b>Comparable KINAVET-CA1 Tablet Dose <sup>a</sup></b>	<b>Number of Dogs</b>
Group 1 (Control)	0 mg/kg (normal saline)	5 males and 5 females
Group 2	10.5 mg/kg	3 males and 3 females
Group 3	35.1 mg/kg	3 males and 3 females
Group 4	105.5 mg/kg	5 males and 5 females

<sup>a</sup> Masitinib was administered as a solution in saline

Drug Administration: Dogs were dosed by gavage once daily at the specified dose for 4 weeks. At the end of the treatment period, two males and two females of the control and the 35.1 mg/kg and 105.5 mg/kg groups were evaluated for a 2-week treatment-free recovery period.

Measurements and Observations: The dogs were monitored for mortality, clinical signs, body weight, food consumption, ophthalmic changes, electrocardiograph recordings, hematological, blood biochemical, bone marrow evaluation, toxicokinetics, and urinalysis. On completion of the treatment or treatment-free period, designated dogs were euthanized and underwent full macroscopic examination, designated organs were weighed and selected tissue specimens were preserved for microscopic examination.

Statistical Methods: Absolute organ weights and body weight gain (at the end of the treatment period compared to the beginning) were analyzed using an analysis of variance. The terms in the model were dose group, sex, and dose group by sex (except for testes). Variables that had baseline values measured, such as clinical pathology and heart rate, were analyzed using analysis of covariance. The terms in the model were the dose group, sex, dose group by sex, and baseline. For the 8 dogs (4 in Group 1, and 4 in Group 4) that went through the treatment-free period, only the data collected during the treatment period were used in the analysis.

f) Results

Dose related trends for clinical signs are shown in Table 6.

Table 6: Incidence of Clinical Signs in the 4-Week Toxicity Study

Clinical Sign	Group 1 (n=10)	Group 2 <sup>a</sup> (n=6)	Group 3 <sup>a</sup> (n=6)	Group 4 <sup>a</sup> (n=10)
Pallor	0	0	5	10
Soft stool to diarrhea				
Incidence	0	2	4	10
Frequency in affected dogs		1-2x/dog <sup>b</sup>	1-3x/dog	2-8x/dog
Blood-tinged feces	0	0	0	4
Vomiting or regurgitation				
Incidence	0	2	6	10
Frequency in affected dogs		2-3x/dog	4-11x/dog	12-23x/dog
Excessive salivation <sup>c</sup>				
Incidence	0	2	6	10
Frequency in affected dogs		2-3x/dog	8-18x/dog	10-20x/dog
Lethargy	0	1 (< 1 day)	0	1 (3 days)
Weight loss >5%, Day 1-28	0	0	0	4
Death	0	0	0	1 <sup>d</sup>

<sup>a</sup> Groups 2, 3, and 4 were treated with daily doses of masitinib solution comparable to KINAVET-CA1 tablet doses of 10.5 mg/kg, 35.1 mg/kg, and 105.5 mg/kg, respectively.

<sup>b</sup> Frequency in affected dogs denoted as 1-2x/dog means: 1 to 2 times per dog.

<sup>c</sup> Excessive salivation was related to gavage of masitinib solution.

<sup>d</sup> The dog that became recumbent and died on Day 29 had lesions compatible with aspiration (acute esophagitis and pneumonitis).

Dose related trends in selected clinical pathology test results are shown in Table 7.

Table 7: Incidence of Selected Clinical Pathology Results<sup>a</sup> in the 4-Week Toxicity Study

Variable	Group 1 (n=10)	Group 2 (n=6)	Group 3 (n=6)	Group 4 (n=10)
Anemia incidence and severity <sup>b</sup>	0	1 mild	1 moderate 3 mild	1 moderate 4 mild
Neutropenia incidence and severity <sup>c</sup>	0	1 mild	2 moderate 4 mild	1 moderate 2 mild
Hypoalbuminemia incidence and severity <sup>d</sup>	0	0	2 mild	2 moderate 7 mild
Elevated fibrinogen or APTT (activated partial thromboplastin time)	0	0	0	1 fibrinogen 1 APTT
Elevated AST & ALT <sup>e</sup>	0	0	0	1 mild
Proteinuria reported in dogs with no proteinuria at baseline <sup>f</sup>	0	0	1 low	1 moderate 5 low
Hematuria reported in dogs with no hematuria at baseline <sup>g</sup>	0	0	0	1 high 1 moderate 2 low

<sup>a</sup> Results at the end of the 4-week treatment period

<sup>b</sup> Anemia severity: mild = hemoglobin (Hb) <12-10 g/dL, moderate = Hb <10-8 g/dL

<sup>c</sup> Neutropenia severity: mild =  $2.0-3.0 \times 10^3 \mu\text{L}$ , moderate =  $1.0-1.9 \times 10^3 \mu\text{L}$

<sup>d</sup> Hypoalbuminemia severity: mild = 2.1-2.7 g/dL, moderate = 1.5-2.0 g/dL

<sup>e</sup> Elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were mild; both were less than 2 times the upper limit of the normal range.

<sup>f</sup> Proteinuria by dipstick test: low = 0.3 g/L, moderate = 1.0 g/L, high =  $\geq 3.0 \text{ g/L}$ . In these cases, proteinuria occurred in urine samples that did not have red or white blood cells on microscopic examination of the urine sediment.

<sup>g</sup> Hematuria was determined by dipstick test. Bilirubinuria was also increased in Group 4.

Statistically significant results at the end of the treatment period are shown in Table 8.

Table 8: Statistically Significant Results in the 4-Week Toxicity Study <sup>a</sup>

Variables	Treated vs. Control
Body weight gain	Group 4 < Group 1
Heart Rate	Group 4 > Group 1
<b>Hematology</b>	
Red Blood Cell Count (RBC)	Groups 2, 3 & 4 < Group 1
Hemoglobin (Hb)	Groups 2, 3 & 4 < Group 1
Packed Cell Volume (PCV)	Groups 2, 3 & 4 < Group 1
MCV <sup>b</sup>	Groups 2, 3 & 4 < Group 1
MCHC <sup>b</sup>	Groups 3 & 4 > Group 1
Neutrophil Count	Groups 2, 3 & 4 < Group 1
White Blood Cell Count (WBC)	Groups 2, 3 & 4 < Group 1
Eosinophil Count	Groups 3 & 4 < Group 1
<b>Coagulation</b>	
Fibrinogen	Group 4 > Group 1
Activated Partial Thromboplastin Time (APTT)	Group 4 > Group 1
<b>Biochemistry</b>	
Total protein	Groups 3 and 4 < Group 1
Albumin	Groups 3 and 4 < Group 1
Calcium	Groups 3 and 4 < Group 1
Creatine Kinase	Groups 3 and 4 > Group 1
Chloride	Groups 3 and 4 > Group 1
Glucose	Groups 3 and 4 > Group 1
Urea Nitrogen (BUN)	Group 4 > Group 1
Alkaline Phosphatase (ALP)	Group 4 > Group 1
Alanine Aminotransferase (ALT)	Group 4 > Group 1
<b>Absolute Organ Weight</b>	
Thymus Weight	Group 4 < Group 1

<sup>a</sup> Results at the end of the 4-week treatment period, p-values < 0.1

<sup>b</sup> Decreased MCV (mean corpuscular volume) and increased MCHC (mean corpuscular hemoglobin concentration) are consistent with a non-regenerative anemia.

Histopathologic lesions primarily involved the liver, bone marrow, and lymphatic tissue. Dose related trends in histopathology results are shown in Table 9.

Table 9: Incidence of Selected Histopathology Results<sup>a</sup> in the 4-Week Toxicity Study

Histopathology	Incidence and Severity			
	Group 1 (n=6)	Group 2 (n=6)	Group 3 (n=6)	Group 4 (n=6)
Vacuolated hepatocytes <sup>b</sup>	1 minimal	0	1 minimal	1 marked 1 moderate
Vacuolated Kupffer cells <sup>b</sup>	0	0	1 slight 3 minimal	1 marked 2 moderate 2 slight 1 minimal
Brownish pigment laden Kupffer cells	0	0	2 minimal	5 minimal
Bile canicular plugs	0	0	4 minimal	3 slight 3 minimal
Bone marrow hypo-cellularity <sup>c</sup>	0	0	1 marked 3 moderate 2 slight	2 marked 2 moderate 2 slight
Bone marrow lipid tissue <sup>c</sup>	6 minimal	1 slight 5 minimal	4 marked 2 moderate	4 marked 2 moderate
Lymphoid depletion of the thymus	1 moderate 1 slight	4 minimal	1 slight 3 minimal	2 marked 1 slight 2 minimal
Foamy macrophages in the mesenteric lymph node (LN)	0	0	5 minimal	2 slight 3 minimal
Decreased germinal centers in the mandibular LN	0	0	0	2 slight
Lymphoid depletion of the spleen	0	0	0	1 slight
Histiocytosis of the spleen	0	0	0	2 slight 2 minimal
Foamy alveolar (lung) macrophages	0	3 minimal	2 minimal	3 slight 2 minimal
Acute esophagitis	0	0	1 slight	1 marked 1 moderate

<sup>a</sup> Results of dogs necropsied at the end of the 4-week treatment period

<sup>b</sup> Of the six Group 4 dogs necropsied at the end of the 4-week treatment period, three had grossly enlarged livers with moderate to marked vacuolization of hepatocytes and/or Kupffer cells on histopathology.

<sup>c</sup> Bone marrow histopathology is consistent with bone marrow cytology on dogs necropsied at the end of the 4-week treatment period, which showed a dose dependent increase in the myeloid to erythroid ratio.

On completion of the 2-week recovery period, a partial reversibility was noted in animals from Group 4. See Table 10.

Table 10: Clinical Findings at the End of the 2-Week Recovery Period

Findings	Incidence	
	Group 1 (n=4)	Group 4 (n=4)
Pallor	0	4
Anemia, mild	0	1
Regenerative anemia, mild (increased reticulocyte count)	0	4
Increased platelet count, mild	0	1
Hypoalbuminemia, mild	0	1
Grey/green colored livers at necropsy with bile canalicular plugs on histopathology	0	3
Liver brownish pigment laden macrophages, minimal	0	3
Liver brownish pigment laden Kupffer cells, minimal	0	1
Vacuolated Kupffer cells, minimal	0	1
Enlarged spleen	0	4

Plasma Levels of Masitinib: On the first day of dosing, plasma masitinib exposure increased with dose, but the increases in  $C_{max}$  and AUC were less than proportional over the three doses tested. This study tested doses comparable to KINAVET-CA1 tablet doses of 10.5 mg/kg (Group 2), 35.1 mg/kg (Group 3), and 105.5 mg/kg (Group 4). Inter-animal coefficients of variation in  $C_{max}$  ranged 8 to 28% and inter-animal coefficients of variation in AUC ranged 9 to 70%.

After 28 days of dosing, the increases in  $C_{max}$  and AUC were nearly proportional across the Group 2 and 3 dose range because plasma masitinib accumulation was observed (at least 26%) in Group 3. Inter-animal coefficients of variation in  $C_{max}$  ranged 14 to 19% and inter-animal coefficients of variation in AUC ranged 14 to 32%. Significant plasma masitinib accumulation ( $\geq 46\%$  on average) was observed in Group 4 after 28 days. A gender effect was not noted.

- g) Conclusions for the 4-Week Toxicity Study: Transient and occasional vomiting, soft feces, and lethargy occurred at a dose comparable to 0.7X the maximum label dose of 15.0 mg/kg/day. At doses comparable to 2.3X and 7X the maximum label dose, dogs had a dose-dependent increase in the incidence and severity of gastrointestinal signs (vomiting, diarrhea, blood in the feces), bone marrow suppression (hypocellularity, non-regenerative anemia, pallor, and neutropenia), proteinuria and hypoalbuminemia without associated kidney lesions on histopathology, liver abnormalities (mildly increased liver enzymes, histopathologic lesions), lymphatic tissue toxicity (lymphoid depletion and other



histopathologic lesions), and increased coagulation values. Treatment related effects were partially reversible after a 2-week treatment-free recovery period.

### C. 13-Week Toxicity Study

- a) Study Title and Number: 13-Week Toxicity Study By Oral Route (Gavage) In Beagle Dogs Followed by a 4-Week Treatment-Free Period, Study No. 24373 TCC
- b) Type of Study: GLP laboratory study
- c) Study Dates: June – October 2003
- d) Study Director and Location: Isabelle Gaou, CIT, Evreux, France
- e) General Design

Purpose of Study: To evaluate the potential toxicity of an oral solution of masitinib, administered daily for 13 weeks, and the potential reversibility of findings after a subsequent 4-week treatment-free recovery period.

Study Animals: Thirty-two Beagle dogs (approximately 6 months of age) were randomly allocated to three test item groups and one control group. One Group 4 dog died on Day 8 and was replaced by another dog.

#### Treatment Groups:

Table 11: Treatment Group Doses for the 13-Week Toxicity Study

Treatment Group	Comparable KINAVET-CA1 Tablet Dose <sup>a</sup>	Number of Dogs
Group 1 (Control)	0 mg/kg(normal saline)	5 males and 5 females
Group 2	3.5 mg/kg	3 males and 3 females
Group 3	10.5 mg/kg	3 males and 3 females
Group 4	35.1 mg/kg	5 males and 5 females

<sup>a</sup> Masitinib was administered as a solution in saline

Drug Administration: Dogs were dosed by gavage once daily at the specified dose for 13 weeks. At the end of the treatment period, two males and two females of the control and high-dose groups were evaluated for a 4-week treatment-free recovery period.

**Measurements and Observations:** The dogs were monitored for mortality, clinical signs, body weight, food consumption, ophthalmology examinations, electrocardiograph recordings, hematological, blood biochemical investigations, toxicokinetics, and urinalysis. On completion of the treatment or treatment-free period, designated dogs were euthanized and underwent full macroscopic examination, designated organs were weighed and selected tissue specimens were preserved for microscopic examination.

**Statistical Methods:** Absolute organ weights and body weight gain (at the end of the treatment period compared to the beginning) were analyzed using an analysis of variance. The terms in the model were dose group, sex, and dose group by sex (except for testes). Variables that had baseline values measured, such as clinical pathology and heart rate, were analyzed using analysis of covariance. The terms in the model were the dose group, sex, dose group by sex, and baseline. For the 8 dogs (4 in Group 1, and 4 in Group 4) that went through the treatment-free period, only the data collected during the treatment period were used in the analysis.

f) Results

Dose related trends in clinical signs are shown in Table 12.

Table 12: Incidence of Clinical Signs in the 13-Week Toxicity Study

Clinical Sign	Group 1 (n=10)	Group 2 <sup>a</sup> (n=6)	Group 3 <sup>a</sup> (n=6)	Group 4 <sup>a</sup> (n=11)
Pallor	0	0	0	9
Soft stool to diarrhea				
Incidence	5	4	1	7
Frequency in affected dogs	1-5x/dog	1-3x/dog	3x/dog	2-7x/dog
Vomiting or regurgitation				
Incidence	0	0	3	9
Frequency in affected dogs			1-3x/dog	1-4x/dog
Excessive salivation <sup>b</sup>				
Incidence	0	1	4	10
Frequency in affected dogs		1x/dog	1-6x/dog	≥ 20x/dog
Lethargy or weakness	0	0	1	2
Erythema of muzzle	0	0	1	0
Death	0	0	0	1 <sup>c</sup>

<sup>a</sup> Groups 2, 3, and 4 were treated with daily doses of masitinib solution comparable to KINAVET-CAI tablet doses of 3.5 mg/kg, 10.5 mg/kg, and 35.1 mg/kg, respectively.

<sup>b</sup> Excessive salivation was related to gavage of masitinib solution.

<sup>c</sup> The Group 4 dog died shortly after dosing on Day 8 had lesions compatible with aspiration (reddish colored lungs and foamy contents in the trachea and lungs). She was replaced with another female that underwent all procedures 8 days after the rest of the dogs in her group.

Dose related trends in selected clinical pathology test results are shown in Table 13.

Table 13: Incidence of Selected Clinical Pathology Results <sup>a</sup> in the 13-Week Toxicity Study

Variable	Incidence and Severity			
	Group 1 (n=10)	Group 2 (n=6)	Group 3 (n=6)	Group 4 (n=6)
Anemia <sup>b</sup>	0	0	1 mild	1 moderate 6 mild
Neutropenia <sup>c</sup>	0	0	0	1 moderate 6 mild
Hypoalbuminemia <sup>d</sup>	0	0	0	2 mild
Elevated fibrinogen or APTT (activated partial thromboplastin time)	0	0	0	1 fibrinogen 1 APTT
Elevated alkaline phosphatase (ALP) <sup>e</sup>	0	0	0	1 mild
Elevated blood glucose <sup>f</sup>	0	0	0	1 moderate

<sup>a</sup> Results during or at the end of the 13-week treatment period

<sup>b</sup> Anemia severity: mild = Hb <12-10 g/dL, moderate = Hb <10-8 g/dL

<sup>c</sup> Neutropenia severity: mild =  $2.0-3.0 \times 10^3 \mu\text{L}$ , moderate =  $1.0-1.9 \times 10^3 \mu\text{L}$

<sup>d</sup> Hypoalbuminemia severity: mild = 2.1-2.7 g/dL, moderate = 1.5-2.0 g/dL

<sup>e</sup> ALP elevation was mild, less than 2 times the upper limit of the normal range

<sup>f</sup> Glucose was moderately elevated, at 190 mg/dL

Statistically significant results at the end of the treatment period are shown in Table 14.

Table 14: Statistically Significant Results in the 13-Week Toxicity Study<sup>a</sup>

Variables	Treated vs. Control
<b>Hematology</b>	
Red Blood Cell Count (RBC)	Groups 3 & 4 < Group 1
Hemoglobin (Hb)	Groups 3 & 4 < Group 1
Packed Cell Volume (PCV)	Groups 3 & 4 < Group 1
MCV <sup>b</sup>	Groups 3 & 4 > Group 1
MCHC <sup>b</sup>	Groups 3 & 4 < Group 1
Neutrophil Count	Group 4 < Group 1
White Blood Cell Count (WBC)	Group 4 < Group 1
Eosinophil Count	Group 4 < Group 1
Platelet Count	Group 4 > Group 1
<b>Coagulation</b>	
Fibrinogen	Group 4 > Group 1
Activated Partial Thromboplastin Time (APTT)	Groups 3 & 4 > Group 1
<b>Biochemistry</b>	
Albumin	Group 4 < Group 1
Calcium	Group 4 < Group 1
Potassium	Group 4 > Group 1
Chloride	Group 4 > Group 1
Alkaline Phosphatase (ALP)	Group 4 > Group 1
Alanine Aminotransferase (ALT)	Group 4 > Group 1
<b>Absolute Organ Weight</b>	
Liver Weight	Groups 3 & 4 > Group 1

<sup>a</sup> Results at the end of the 13-week treatment period, p-values < 0.1

<sup>b</sup> Increased MCV (mean corpuscular volume) and decreased MCHC (mean corpuscular hemoglobin concentration) are opposite from the 4-week toxicity study results (Study No. 24371 TSC).

Histopathologic lesions primarily involved the liver, gall bladder, bone marrow, and lungs. Dose related trends in histopathology results are shown in Table 15.

Table 15: Incidence of Selected Histopathology Results<sup>a</sup> in the 13-Week Toxicity Study

Lesions	Incidence and Severity			
	Group 1 (n=6)	Group 2 (n=6)	Group 3 (n=6)	Group 4 (n=6)
Hepatocellular hypertrophy	0	0	0	2 slight 4 minimal
Brownish pigment laden Kupffer cells	0	0	0	1 slight
Gall bladder cystic epithelial hyperplasia	0	0	0	2 slight
Bone marrow lipoid tissue	1 moderate 2 slight 1 minimal	1 slight 3 minimal	1 moderate 1 slight 3 minimal	3 marked 2 minimal
Chronic interstitial pneumonitis	1 minimal	0	0	2 moderate

<sup>a</sup> Results of dogs necropsied at the end of the 13-week treatment period

On completion of the 4-week recovery period, the adverse findings previously recorded for dogs in Group 4 were no longer observed.

Plasma Levels of Masitinib: On the first day of dosing plasma masitinib exposure increased with dose and appeared to be dose proportional over the three doses tested. This study tested doses comparable to KINAVET-CA1 tablet doses of 3.5 mg/kg (Group 2), 10.5 mg/kg (Group 3), and 35.1 mg/kg (Group 4). Inter-animal coefficients of variation in  $C_{max}$  ranged 35 to 56% and inter-animal coefficients of variation in AUC ranged 38 to 59%.

After 13 weeks of daily dosing increases in  $C_{max}$  and AUC were more than dose proportional for Group 3 and Group 4 compared to Group 2. However,  $C_{max}$  and AUC values were proportional in Groups 3 and 4. Inter-animal coefficients of variation in  $C_{max}$  ranged 19 to 95% and inter-animal coefficients of variation in AUC ranged 23 to 101%. Plasma masitinib exposure accumulation was variable (20 to > 200 %) in Groups 3 and 4 after 13 weeks of daily dosing. A gender effect was not noted.

- g) Conclusions for the 13-Week Toxicity Study: Transient and occasional vomiting, muscle weakness, erythema of the muzzle, and mild anemia occurred at a dose comparable to 0.7X the maximum label dose of 15.0 mg/kg/day. At a dose comparable to 2.3X the maximum label dose, dogs had vomiting, diarrhea, lethargy, and mild hypoalbuminemia. The dogs also had evidence of bone marrow suppression (increased lipoid tissue in the bone marrow, anemia, pallor,

and neutropenia), liver abnormalities (mildly increased liver enzymes, histopathologic lesions), and increased coagulation values. Treatment related effects were no longer observed (reversed) after a 4-week treatment-free recovery period.

#### D. 39-Week Toxicity Study

- a) Study Title and Number: 39-Week Toxicity Study By Oral Route (Gavage) In Beagle Dogs, Study No. 26100 TCC.
- b) Type of Study: GLP laboratory study
- c) Study Dates: August 2003 – May 2004.
- d) Study Director and Location: Isabelle Gaou, CIT, Evreux, France
- e) General Design

Purpose of Study: To evaluate the potential toxicity and pharmacokinetics of an oral solution of masitinib, administered daily for 39 weeks.

Study Animals: Thirty-two Beagle dogs (approximately 7 months of age) were randomly allocated to three test item groups and one control group of 4 males and 4 females each.

#### Treatment Groups:

Table 16: Treatment Group Doses for the 39-Week Toxicity Study

Treatment Group	Comparable KINAVET-CA1 Tablet Dose <sup>a</sup>	Number of Dogs
Group 1 (Control)	0 mg/kg (normal saline)	4 males and 4 females
Group 2	2.1 mg/kg	4 males and 4 females
Group 3	7.0 mg/kg	4 males and 4 females
Group 4	20.9 mg/kg	4 males and 4 females

<sup>a</sup> Masitinib was administered as a solution in saline

Drug Administration: Dogs were dosed by gavage daily at the specified level for 39 weeks.

Measurements and Observations: The dogs were monitored for mortality, clinical signs, body weight, food consumption, ophthalmology examinations, electrocardiograph recordings, hematological, blood biochemical investigations, toxicokinetics, and urinalysis. On completion of the treatment period, the dogs

were euthanized and underwent full macroscopic examination, designated organs were weighed and selected tissue specimens were preserved for microscopic examination.

Statistical Methods: Absolute organ weights and body weight gain (at the end of the study compared to the beginning) were analyzed using an analysis of variance. The terms in the model were dose group, sex, and dose group by sex (except for testes). Variables which were measured multiple times during the study (including baseline measurements), such as clinical pathology and heart rate, were analyzed using a repeated measures analysis of covariance. The terms in the model were dose group, study day, sex, all their two- and three-way interactions, and baseline.

f) Results

Mortality: One Group 4 female was euthanized prematurely on Day 225 (Week 33). During the weeks preceding euthanasia, she developed a swollen abdomen due to ascites, emaciated appearance, pallor, decreased appetite, lethargy, loss of balance, tremors, lateral recumbency, severe anemia, marked thrombocytosis, lymphopenia, increased APTT and fibrinogen, severe hypoalbuminemia and hypoproteinemia, increased blood urea nitrogen and creatine kinase, severe proteinuria, hematuria without red cells, and decreased urine pH. Histopathology findings included edema in the pericardium, thymus, subcutaneous tissue, pancreas and adjacent lymph nodes, and severe lymphoid depletion in the thymus.

Dose related trends in clinical signs are shown in Table 17.

Table 17: Incidence of Clinical Signs in the 39-Week Toxicity Study

Clinical Sign	Group 1 (n=8)	Group 2 <sup>a</sup> (n=8)	Group 3 <sup>a</sup> (n=8)	Group 4 <sup>a</sup> (n=8)
Pallor	0	0	1	8
Soft stool to diarrhea				
Incidence	4	0	4	6
Frequency in affected dogs	1-5x/dog		1-2x/dog	1-3x/dog
Vomiting or regurgitation				
Incidence	1	1	2	6
Frequency in affected dogs	1x	1x	1-4x/dog	1-3x/dog
Excessive salivation <sup>b</sup>				
Incidence	1	3	8	8
Frequency in affected dogs	1x	1-3x/dog	1-12x/dog	≥ 68x/dog
Lethargy	0	0	2	3
Lateral recumbency	0	0	0	2
Hind leg stiffness	0	0	0	1
Erythema of the neck	0	0	1	2
Depigmentation of eyelids	0	0	0	1
Reported to be emaciated in the last 3 weeks of the study	1	2	0	4
Death	0	0	0	1 <sup>c</sup>

<sup>a</sup> Groups 2, 3, and 4 were treated with daily doses of masitinib solution comparable to KINAVET-CA1 tablet doses of 2.1 mg/kg, 7.0 mg/kg, and 20.9 mg/kg, respectively.

<sup>b</sup> Excessive salivation was related to gavage of masitinib solution.

<sup>c</sup> The dog that was euthanized in Week 33 is described above.



Dose related trends in selected clinical pathology test results are shown in Table 18.

Table 18: Incidence of Selected Clinical Pathology Results <sup>a</sup> in the 39-Week Toxicity Study

Variable	Group 1 (n=8)	Group 2 (n=8)	Group 3 (n=8)	Group 4 (n=8)
Anemia <sup>b</sup> : Incidence and Severity	0	0	2 mild	1 very severe 6 mild
Neutropenia <sup>c</sup> : Incidence and Severity	0	0	0	4 mild
Hypoalbuminemia <sup>d</sup> : Incidence and Severity	0	0	0	1 severe 2 mild
Elevated Fibrinogen or APTT (Activated partial thromboplastin time)	0	0	0	2 Fibrinogen 1 APTT
Proteinuria reported in dogs with no proteinuria at baseline <sup>e</sup>	0	1 low	3 low	2 high 3 low

<sup>a</sup> The worst result reported for each dog during the 39-week study

<sup>b</sup> Anemia: mild = Hb <12-10 g/dL. The dog with very severe anemia had a Hb of 3.9 g/dL prior to euthanasia in Week 33.

<sup>c</sup> Neutropenia: mild = 2.0-3.0 x 10<sup>3</sup> µL, moderate = 1.0-1.9 x 10<sup>3</sup> µL

<sup>d</sup> Hypoalbuminemia: mild = 2.1-2.7 g/dL, moderate = 1.5-2.0 g/dL, severe < 1.5 g/dL

<sup>e</sup> Proteinuria by dipstick test: low = 0.3 g/L, moderate = 1.0 g/L, high = ≥ 3.0 g/L. In these cases, proteinuria occurred in urine samples that did not have red or white blood cells on microscopic examination of the urine sediment.

Statistically significant results are shown in Table 19.

Table 19: Statistically Significant Results in the 39-Week Toxicity Study <sup>a</sup>

Variables	Treated vs. Control
<u>Dose group*day significant for hematology and coagulation</u>	
RBC	Groups 3 & 4 < Group 1 at Weeks 13, 25, and 38
Hemoglobin	Groups 3 & 4 < Group 1 at Weeks 13, 25, and 38
PCV	Groups 3 & 4 < Group 1 at Weeks 13, 25, and 38
MCV <sup>b</sup>	Group 3 > Group 1 at Week 13 Group 4 > Group 1 at Weeks 13, 25, and 38
Neutrophil Count	Group 3 < Group 1 at Weeks 25 and 38 Group 4 < Group 1 at Weeks 13, 25, and 38
Eosinophil Count	Group 4 < Group 1 at Week 38
<u>Dose group main effect significant for hematology and coagulation</u>	
MCHC <sup>b</sup>	Groups 3 & 4 < Group 1
WBC	Group 4 < Group 1
Platelets	Group 4 > Group 1
APTT	Group 4 > Group 1
Prothrombin time	Group 4 > Group 1
<u>Dose group main effect significant for biochemistry</u>	
Total protein	Groups 3 & 4 < Group 1
Albumin	Group 4 < Group 1
Calcium	Group 4 < Group 1
<u>Dose group*day significant for biochemistry</u>	
Sodium	Groups 3 & 4 < Group 1 at Week 38
Glucose	Group 4 > Group 1 at Weeks 13 and 25
<u>Dose group main effect significant for absolute organ weight</u>	
Heart Weight <sup>c</sup>	Groups 2, 3 & 4 > Group 1

<sup>a</sup> p-values < 0.1

<sup>b</sup> Increased MCV (mean corpuscular volume) and decreased MCHC (mean corpuscular hemoglobin concentration) are consistent with the 13-week study results, but the opposite of the 4-week study results.

<sup>c</sup> Mean absolute organ weights excluding the Group 4 female euthanized at Week 33

Histopathologic lesions primarily involved the spleen, liver, bone marrow, and lymphatic tissue. Dose related trends in histopathology results are shown in Table 20.

Table 20: Incidence of Selected Histopathology Results in the 39-Week Toxicity Study

Lesions	Incidence and Severity			
	Group 1 (n=8)	Group 2 (n=8)	Group 3 (n=8)	Group 4 (n=8)
Generalized edema	0	0	0	1 <sup>a</sup>
Increased iron deposits in the spleen (hemosiderosis)	1 slight 6 minimal	5 slight 3 minimal	5 moderate 2 slight 1 minimal	4 marked 4 moderate
Brownish pigment laden Kupffer cells <sup>b</sup>	0	0	2 minimal	1 moderate 3 slight 3 minimal
Liver positive for iron	0	1 minimal	2 minimal	3 minimal
Mandibular lymph node positive for iron	0	2 minimal	4 minimal	5 minimal
Bone marrow lipoid tissue	3 slight 5 minimal	3 moderate 3 slight 2 minimal	2 marked 3 moderate 2 slight 1 minimal	4 marked 4 moderate
Lymphoid depletion of the thymus <sup>c</sup>	1 moderate 5 slight 2 minimal	3 moderate 3 minimal	4 moderate 2 minimal	1 massive 1 marked 2 moderate 2 slight 2 minimal
Vacuolated seminiferous tubules and oligospermia	0/4 males	0/4 males	0/4 males	2/4 males (slight to moderate)

<sup>a</sup> The dog that was euthanized at Week 33 had ascites, subcutaneous edema, and edema of the thymus, pancreas and associated lymph nodes.

<sup>b</sup> One Group 4 male had an enlarged grey/green colored liver on gross necropsy.

<sup>c</sup> On gross necropsy, small thymus glands were reported in 2/8 Group 1, 1/8 Group 2, 2/8 Group 3, and 4/8 Group 4 dogs.

**Plasma Levels of Masitinib:** On the first day of dosing, the plasma masitinib exposure increased with dose; based on the Group 2 dose the increase in  $C_{max}$  and AUC values was more than dose proportional after the first dose. However, the increases in  $C_{max}$  and AUC appear to be proportional across the Group 3 and 4 dose range. This study tested doses comparable to KINAVET-CA1 tablet doses of 2.1 mg/kg (Group 2), 7.0 mg/kg (Group 3), and 20.9 mg/kg (Group 4). Inter-animal coefficients of variation in  $C_{max}$  ranged 20 to 39% and inter-animal coefficients of variation in AUC ranged 25 to 41%.

After 39 weeks of exposure the  $C_{max}$  and AUC values at higher doses appear to decrease compared to the Group 2 dose because exposure accumulation was

observed in Group 2. Exposure accumulation was not observed in Groups 3 or 4. This observation is in agreement with the results for Group 2 in the 4-week toxicity study, which was treated with a dose comparable to a KINAVET-CA1 tablet dose of 10.5 mg/kg. Inter-animal coefficients of variation in  $C_{max}$  ranged 24 to 59% and inter-animal coefficients of variation in AUC ranged 23 to 38%. A gender effect was not noted.

- g) Conclusions for the 39-Week Toxicity Study: Vomiting, lethargy, erythema of the neck, mild anemia, proteinuria, hemosiderosis of the spleen, and increased lipid tissue in the bone marrow occurred at a dose comparable to 0.5X the maximum label dose of 15.0 mg/kg/day. At a dose comparable to 1.4X the maximum label dose, a dog was euthanized because of severe anemia, hypoproteinemia, proteinuria, pericardial effusion, ascites, emaciated appearance, and lateral recumbency. In that dose group, masitinib toxicity was characterized by gastrointestinal signs (vomiting, diarrhea), general signs (lethargy, hind leg stiffness, erythema of the neck), bone marrow suppression (increased lipid tissue in the bone marrow, anemia, pallor, and neutropenia), evidence of red blood cell sequestration (hemosiderosis of the spleen), proteinuria and hypoalbuminemia without associated kidney lesions on histopathology, liver abnormalities (histopathologic lesions), lymphatic tissue toxicity (lymphoid depletion), and increased coagulation values.

#### **IV. HUMAN FOOD SAFETY:**

This drug is intended for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

#### **V. USER SAFETY:**

The product labeling contains the following information regarding safety for humans handling, administering, or exposed to KINAVET-CA1:

**NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.** Children should not come into contact with KINAVET-CA1. Keep children away from feces, urine, or vomit of treated dogs.

To avoid exposure to drug, wash hands with soap and water after administering KINAVET-CA1 and wear protective gloves to prevent contact with feces, urine, vomit, and broken or crushed KINAVET-CA1 tablets. Place all waste material in a plastic bag and seal before general disposal. If eyes are accidentally exposed to the drug, rinse eyes with water immediately. In case of accidental ingestion by a person, seek medical advice immediately, show the package insert or label to the physician.

Pregnant women, women who may become pregnant, or nursing mothers should pay special attention to these handling precautions (see handling instructions above). KINAVET-CA1 may harm an unborn baby (cause birth defects). For pregnant and nursing women, accidental ingestion of KINAVET-CA1 may have adverse effects on pregnancy or the nursing baby.

## **VI. AGENCY CONCLUSIONS:**

The data submitted in support of this application satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act. The data demonstrate that KINAVET-CA1, when used according to the label, is safe and has a reasonable expectation of effectiveness for the treatment of recurrent (post-surgery) or nonresectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and/or chemotherapy except corticosteroids.

### **A. Marketing Status:**

KINAVET-CA1 is conditionally approved for one year from the date of approval and is annually renewable for up to four additional one-year terms.

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to properly diagnose mast cell tumors and to monitor safe use of the product, including treatment of any adverse reactions.

### **B. Exclusivity:**

KINAVET-CA1 in the dosage form and for the intended uses conditionally approved by FDA under application number 141-308 qualifies for seven years of exclusive marketing rights beginning as of the date of conditional approval. This new animal drug qualifies for exclusive marketing rights under section 573(c) of the Federal Food, Drug, and Cosmetic Act (the act) because it has been declared a designated new animal drug by FDA under section 573(a) of the act.

### **C. Patent Information:**

KINAVET-CA1 is under the following U.S. patent numbers:

<u>U.S. Patent Number</u>	<u>Date of Expiration</u>
7,423,055	August 1, 2023

For current information on patents, see the Animal Drugs @ FDA database (formerly the Green Book) on the FDA CVM internet website.

**VII. ATTACHMENTS:**

Labeling:  
Package Insert  
Client Information Sheet

## EXHIBIT H



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

INAD 011206 A-0000

AB Science  
Attention: Anne-Virginie Eggimann, M.Sc.  
Consultant  
38 rue Vauthier  
92100 Boulogne  
France

MAR 11 2004

Dear Ms. Eggimann:

We refer to your submission dated November 24, 2003, (A-0000), wherein you requested an Investigational New Animal Drug (INAD) exemption for the use of AB1010. The drug product is proposed for the treatment of mast cell tumors in dogs. Your submission also requested a presubmission conference to discuss the development of your product in the United States. Under cover letter dated January 5, 2004, (T-0001) you submitted a request for a categorical exclusion from preparing an environmental assessment.

For administrative purposes, we have assigned you INAD number 011206 for the use of AB1010 in canines. Please refer to this number in all drug shipments and correspondence concerning the drug while it is in the investigational stage. Future correspondence regarding this submission to your INAD file should be identified by the submission's correspondence date and our file number, INAD 011206 A-0000 and submitted directly to the Document Control Unit (HFV-199).

Please find enclosed CVM's minutes from the presubmission conference, which took place on December 18, 2003.

Your claim for the investigational use of AB1010 falls within the categorical exclusion in 21 CFR 25.33(e). Your submission states that to your knowledge, no extraordinary circumstances exist which may significantly affect the human environment. Therefore, neither an environmental assessment (EA) nor an environmental impact statement is required. This categorical exclusion from preparation of an EA and an Environmental Impact Statement does not relieve you of the responsibility for determining and meeting all Federal, State, and local environmental and occupational laws and regulations that apply to the manufacturing, use, and disposal of the investigational drugs.



Prior to shipment of the new animal drug for clinical tests in animals, you must submit in triplicate a "Notice of Claimed Investigational Exemption for a New Animal Drug", in accordance with 21 CFR 511.1(b)(4).

Investigational labeling should be affixed to your investigational drug product prior to shipment for studies conducted under 21 CFR 511.1(a) or (b), as appropriate.

If you have any questions or if you need further assistance, please contact, Elizabeth A. Luddy, Leader, Companion and Wildlife Team. The telephone number is (301) 827-7540.

Sincerely yours,



Melanie R. Berson, DVM  
Director  
Division of Therapeutic Drugs  
for Non-Food Animals  
Office of New Animal Drug Evaluation  
Center for Veterinary Medicine

Enclosure

I-011206-A-0000  
AB1010  
Canine  
AB Science  
38 rue Vauthier  
92100 Boulogne  
France  
December 18, 2003

**Memorandum of Presubmission Conference**  
**December 18, 2003, 1 – 3 pm**

**Attendees:**

**CVM:** Melanie Berson, HFV-110  
Elizabeth Luddy, HFV-112  
Lisa Troutman, HFV-112  
Douglass Oeller, HFV-112  
Anna Nevius, HFV-105  
Marilyn Martinez, HFV-130  
June Liang, HFV-143  
Glen Ghiorghis, HFV-143

**AB Science**

Alain Moussy  
Olivier Hermine  
Des Curran  
Philippe Reginault  
Laurent Guy  
Marie-Paul Lachaud Lefay – ICON  
Leland Vickers – ICON  
Anne-Virgine Eggimann – Consultant  
Emmanuelle Voisin – Consultant

**Background:**

The sponsor provided background information regarding the incidence of Mast Cell Tumors (MCT) in dogs. The histological grading system and survival data associated with the different grades was discussed.

**Drug Characteristics:**

The drug is referred to by two different names. AB1003 is the free base form of the drug. It is the drug referenced for the dosage (i.e., 12.5 mg/kg refers to AB1003). AB1010 is the salt form of the drug and is the final market formulation.

The drug is selective to c-kit and PDGF-beta. It does not interact with other tyrosine kinases thereby possibly reducing toxicity. The sponsor has not encountered any

evidence that there is any multi-drug resistance developed after long-term administration of the drug. There is evidence to suggest that it protects against developing resistance in human CML if there is continual pressure on the cells.

The presence of c-kit varies between patients. However, if c-kit is present, it will be in all cells within a MCT because c-kit is the cause of the mutation creating the tumor.

**Effectiveness:**

The sponsor is planning to conduct a multi-location, uncontrolled field study. The study will enroll 110 dogs with either Grade II or Grade III MCTs with or without previous treatments. Dogs may be enrolled with metastases at the discretion of the investigator. It will be conducted at 24 locations including 12 in the United States, five in the United Kingdom, two in the Netherlands, two in Germany, two in France and one in Slovenia. Two thirds of the cases will come from the United States and the remaining one third from the European countries. Locations in the United States will be with board certified oncologists.

CVM questioned whether a central laboratory will perform the histopathology and the clinical chemistry. The sponsor stated that many of the dogs will have had histopathology conducted prior to consideration for inclusion into the study. If possible, the sponsor will obtain histopathology slides to confirm the diagnosis and grading. It would be very difficult to provide a central pathologist for the study. CVM recommended that the sponsor should address the comparability of the scoring from different pathologists in the protocol. Clinical chemistry analysis will be conducted at a central laboratory in the United States.

CVM strongly suggested the sponsor submit the protocol for review to obtain protocol concurrence prior to starting the study. A dosage rationale should be included with the protocol along with scientific justification and rationale for using complete response (CR) + partial response (PR) > 20% for the success criteria. Scientific justification for conducting an uncontrolled study should also be included. Scientific literature from peer reviewed journals or similar sources, documenting the course of disease if untreated should be utilized to justify a historical control.

CVM suggested that if the sponsor was interested, they should submit a second protocol for extended use. It would allow dogs enrolled in the field study to continue receiving drug after the pivotal field study has been completed.

The sponsor presented their proof of concept. A 6 year old Chow Chow in South Africa had two Grade III MCTs with lymph node involvement. The dog was administered 5 mg/kg BID for 63 days. At the end of 63 days, there was no evidence of MCT's or lymph node involvement.

The sponsor asked if they could stop the study if 17 successes were seen after enrolling 55 patients. CVM stated it would be unlikely that we could concur with the proposal. CVM's regulations do not provide for orphan drug status or conditional approvals. Nor

do we have the legal authority to require additional studies after the initial approval. We need to gather both safety and effectiveness data from the field study. There should be enough dogs treated to provide inferential value.

Interim analysis was also discussed. CVM stated that it is not standard practice for us to allow interim analysis. However, the proposal may be included in the protocol for review.

**Target Animal Safety Studies (Nonclinical Studies):**

The sponsor has conducted multiple nonclinical studies in rats and dogs. A 28-day oral toxicity study was conducted in dogs by administering 0, 15, 50, and 150 mg/kg/day by gavage. It was concluded that the No Observable Adverse Effect Level (NOAEL) is 15 mg/kg. At 15 mg/kg/day, transient vomiting and diarrhea were noted. The NOAEL determination will be used to justify the starting dose in the field study.

Results from the 13-week oral toxicity study in dogs are pending. Dogs were dosed at 0, 4, 12, and 41 mg/kg/day by gavage.

The sponsor is currently conducting a 9-month oral toxicity study in dogs. Dogs were dosed at 0, 5, 15, and 50 mg/kg/day by gavage. CVM stated that this study is needed to obtain an open ended label to allow continual use of the drug. Typically a 6 month target animal safety study is necessary at 1, 3, and 5 times the recommended dosage. CVM stated the 1X dose is considered to be 20 mg/kg/day, the maximum dose administered in the field study. The purpose of administering multiples dosages of the drug is to define the toxic syndrome and therapeutic index. The studies conducted to date and this study may be acceptable to support the target animal safety technical section based upon the toxicities observed at dosages above 20 mg/kg/day. The sponsor is conducting the study for 9 months to support an IND in humans. CVM stated that a pharmacokinetic study is needed to bridge between the liquid formulation used in this study and the final market formulation.

The sponsor stated that the final market formulation will have four tablet sizes, 25, 50, 100, and 150 mg. CVM requested that the sponsor look at the dose range based upon body weight administered in the safety studies and discuss how this reflects upon safety for the field study. The smallest dogs may be receiving the largest dose per weight.

The sponsor provided a statistical justification for the number of animals used in the field study. CVM stated that while we look for statistical significance, it is important to have a sufficient number of cases to provide adequate inferential value about the use of the drug under actual conditions of use in the target population. It will be the first time the drug is used in dogs with mast cell tumors under the direction of multiple investigators. We also obtain additional information regarding the safety of the drug used in various breeds under actual conditions of use, with the owners dosing the dogs. To obtain this additional information, we ask that a minimum of 100 dogs be treated with the drug. The potential for drop outs and early withdrawals should be taken into consideration when determining

the number of animals to be enrolled in the study. The protocol should address the minimum and maximum number of animals enrolled at each site.

CVM stated that the safety data does not need to be submitted prior to conducting the field study. When the target animal safety is submitted, all raw data for the studies intended to support the technical section should be submitted along with any translations, if needed. Summaries of all other safety studies conducted in any species (e.g., human, rat or dog) should be submitted in the data package.

**Minor Use in a Major Species:**

The minor use guidance was discussed. The drug may qualify as a minor use in a major species. Currently, the guidance provides very little additional benefit. However, there is a new law before Congress. If the law passes, it could provide immediate benefits to the sponsor. Currently there is not a definition to determine what would qualify as a minor use in a major species. The sponsor could provide a proposal with scientific justification stating why the drug should be considered a minor use in the major species.

**Expedited Review Status:**

CVM stated that the drug would probably qualify for expedited review status (ERS). Expedited review status would reduce the review time for each submission and move it up higher in the reviewer's queue. Data submissions normally have a review time of 180 days. ERS reduces the review time to 90 days. The sponsor should submit a request for ERS with a scientific justification to support the request. Please see CVM's Policy and Procedure Manual Guide 1243.3120 on our website for additional information.

**Pharmacokinetic Data:**

The sponsor indicated that several pharmacokinetic studies were conducted, including a radiolabel study providing information on the mass balance and tissue distribution of this drug in dogs. They also noted that a bridging study has already begun comparing the oral solution used in the toxicology/target animal safety study versus the proposed final market formulation. That study employs a laboratory batch of the product at a strength their original write-up suggested would not be manufactured for marketing purposes. CVM indicated that executed bridging study employing a laboratory batch of the proposed product would not be acceptable.

Regarding their inquiry as to whether or not in vitro dissolution data can be used in lieu of submitting any in vivo bioequivalence study data, CVM indicated that this option would not be acceptable. Firstly, this product is poorly soluble (based upon traditional Biopharmaceutics Classification System specifications). Accordingly, this drug would be classified as either Class II (highly permeable, poorly soluble) or Class IV (poorly soluble, poorly permeable). If it is a Class II compound, in vitro/in vivo correlations need to be established before in vitro dissolution data can support in vivo bioequivalence. If it is a Class IV compound, this is considered a highly problematic drug and only in vivo bioequivalence studies would suffice. However, they were informed that when conducting the in vivo bridging (bioequivalence) study, in vitro dissolution data will be needed to support the waiver of the need to conduct studies on the other dosage strengths.

The dissolution method should be consistent with that agreed upon by the Division of Manufacturing Technologies (HFV-140).

The sponsor asked if the largest size tablet needs to be used in the in vivo bioequivalence trial. CVM explained that since veterinary medicine doses on a mg/kg basis, such a requirement would necessitate the use of giant breed animals. Such a requirement is not tenable under most study conditions, and therefore CVM asks only that the highest mg/kg dose is administered to medium size animals. In vivo bioequivalence study requirements for the additional tablet strengths are then waived if there is compositional proportionality to the strength tablets that underwent in vivo bioequivalence evaluation and if acceptable in vitro dissolution data are submitted. CVM also told the sponsor that all pivotal pharmacokinetic studies should be conducted with pilot batches (10% of full production scale batches), not laboratory batches. Accordingly, the pivotal bridging study should be conducted using the pilot batch that will undergo stability testing for the Chemistry, Manufacturing and Controls (CMC) portion of this application.

The sponsor was advised to submit a bridging study protocol, along with the proposed dissolution method and method of analysis (which we assume will be the f2 criterion). Since the bridging study is intended solely to cover safety, we are concerned with only the upper bound, not the lower bound. The lower bound pertains to effectiveness, which will be determined on the basis of clinical trials.

One concern expressed by CVM is the potential for food to increase the extent of drug absorption. The sponsor indicated that since the oral solution is ~85% bioavailable, they don't believe that this will be a problem. Nevertheless, the sponsor needs to provide information confirming that unexpectedly high drug concentrations will not occur if the product is administered in the prandial state. If they have data confirming that the drug is nearly 100% bioavailable as the oral solution under fasted condition, this should be provided to CVM to address this issue. In this regard, it should be noted that AB Science stated that rats tended to have more bone marrow effects than did dogs, and that they believe this to be attributable to the higher serum drug concentrations observed in rats.

A final point of concern pertained to dose bands and the exact dosages used in the safety study. The sponsor noted that the product will be coated to minimize owner exposure to the drug. CVM noted that this, by definition, prevents that the tablets be scored. The sponsor agreed to this point. With this in mind, the proposed tablet strengths will result in a wide range of mg/kg doses, depending upon the weight of the dog. AB Science indicated that they are considering the manufacture of an additional (25 mg) dosage strength. CVM recommended that AB Science provide information on the maximum dose within each of the tablet strengths (based upon weight ranges) and that this will be used to determine the adequacy of doses used in the toxicology/target animal safety study.

**CMC:**

Liver powder is added to the inside of the tablet in case a dog bites the tablet they will not be adverse to taking the pill again. The liver powder is not intended for advertising for palatability. The pills will be coated to protect the owners and won't be scored. The liver flavor is inside the pill, not in the coating.

**Phased Review of the INAD:**

Under the INAD, CVM provides for phased review of the technical sections necessary for approval of a new animal drug. The technical sections are:

- Effectiveness
- Target Animal Safety
- CMC
- Environmental Assessment
- Labeling
- Freedom of Information (FOI) Summary
- All Other Information

Each technical section is submitted separately for review. All data to support the technical section is submitted together. The wording for the labeling relevant to the technical section, as well as the component of the FOI Summary are submitted with each technical section. After all technical sections are complete, an Administrative NADA is filed to request approval.

A client information sheet may be included with the labeling. Various formats are acceptable including a question and answer format.

**U.S. Agent:**

Prior to submitting the Administrative NADA, the sponsor should identify a US Agent. All correspondence regarding the NADA will be directed to them. In the meantime, Anne-Virgine Eggimann and Emmanuelle Voisin are the company contacts for correspondence.

Lisa M. Troutman, MS, DVM  
Veterinary Medical Officer, HFV-112

cc: HFV199/INAD 11206 A0000  
LTroutman/HFV112/12-18-03  
Final: gsg/3-10-04  
cc: CVM Records\ONADE\I011206A0000met.min

# EXHIBIT I



# NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION

**PAPERWORK REDUCTION ACT STATEMENT:** A Federal agency may not conduct or sponsor, and a person is not required to respond to, a collection of information, unless it displays a current valid OMB control Number. The public reporting burden for the collection of information is estimated to vary from 15 minutes to 2 hours, with an average of 30 minutes per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary information, and completing and reviewing the collection of information. Send comments regarding the burden estimate or any other aspect of this collection of information to the Food and Drug Administration, Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

**Submit this notice to:**

Food and Drug Administration  
Center for Veterinary Medicine  
Document Control Unit, HFV-199, Room N-403  
(Attention: Review Division HFV- )  
7500 Standish Place  
Rockville, Maryland 20855

DATE: Feb 1<sup>st</sup>, 2005  
INAD / IFA NO: INAD 11206  
STUDY / TRIAL ID: AB1010 PIIMCT 04003  
DRUG SHIPMENT NO: 1  
TYPE OF SHIPMENT: ☒ Initial

☐ Discontinued

☐ Supplement  
☐ Other

The sponsor, AB Science 3 Avenue George V, 75008 Paris, France, submits a notice of claimed investigational exemption for the shipment or delivery of a new animal drug under the provisions of 21 CFR 511.1. This information is submitted in paper (in triplicate).

## I. Shipment X or Receipt ☐ Information

1. NAME(S) OF THE DRUG(S)  
Established name(s): AB 1010  
Trade name(s):
2. PROPOSED USE OF THE DRUG(S): MAST CELL TUMOR TREATMENT
3. DATE OF DRUG SHIPMENT (OR RECEIPT): FEB 03, 2005
4. TOTAL QUANTITY (WT. OR VOL.) AND CONCENTRATION OF DRUG(S) SHIPPED (OR RECEIVED): 32 BOTTLES OF 50 TABLETS  
Each tablet contains 25, 100 or 150 mg AB1010base or is the matching placebo
5. TYPE OF STUDY / TRIAL: DOUBLE-BLIND RANDOMIZED STUDY VS PLACEBO
6. INTENDED USE OF STUDY OR TRIAL: ☒ Pivotal (intended for support of NADA or ANADA) ☐ Non-pivotal
7. NAME AND ADDRESS OF INVESTIGATOR: DAVID ARGYLE  
UNIVERSITY OF WISCONSIN, SCHOOL OF VETERINARY MEDICINE  
2015 LINDEN DRIVE  
MADISON WI 53703-1102  
Phone Number: 608-262-5990
8. LOCATION OF STUDY / TRIAL: UNIVERSITY OF WISCONSIN, SCHOOL OF VETERINARY MEDICINE  
2015 LINDEN DRIVE  
MADISON WI 53703-1102
9. NAME AND ADDRESS OF STUDY MONITOR: DIANE PROBASCO  
  
Phone Number:
10. APPROXIMATE DATE OF STUDY / TRIAL Start: February 2005 Finish: DECEMBER 2005
11. PROTOCOL SUBMITTED TO CVM: ☒ Yes ☐ No  
If Yes, date submitted to CVM and/or CVM submission number: FEB 10, 2005
12. SPECIES OF ANIMALS: DOG
13. SIZE AND TYPE OF ANIMALS: ANY
14. APPROXIMATE NUMBER OF ANIMALS IN THIS STUDY/TRIAL:  
Total: 125 Treated: 100 Control: 25
15. NUMBER OF ANIMALS PREVIOUSLY USED:  
Total: 0 Treated: Control:
16. MAXIMUM DAILY DOSE: 12.5 MG/KG AND DURATION: 6 MONTHS
17. METHOD OF ADMINISTRATION: ORAL ROUTE
18. CONTRACT RESEARCH ORGANIZATIONS (CRO) USED: ☒ Yes ☐ No  
Name and address of CRO: Harrison Clinical Research

Phone Number:  
Description of obligations transferred to CRO: study monitoring

## II. Animals Intended For Human Food Purposes

1. DATE OF CVM AUTHORIZATION LETTER:
2. WITHDRAWAL PERIOD:
3. ACKNOWLEDGEMENT: Acknowledgment that the date and place of slaughter will be reported to FDA and Dr. Julie Cornett, USDA/FSIS, Technical Service Center, 1299 Farnam Street, Suite 300, Landmark Center, Omaha, NE, 68102, at least 10 days prior to shipment for slaughter. Experimentally treated animals will be identified to the inspector in charge of the slaughtering establishment when presented for antemortem inspection.  
☐ Yes ☐ No
4. NOTIFICATION WAIVER: A waiver of requirements for notification of the date and place of slaughter after a 30-day holding and observation period following the required withdrawal period has been granted by FDA.  
☐ Yes ☐ No

## III. Investigational New Animal Drug Labeling (Please select one label)

1. NEW ANIMAL DRUGS FOR TESTS *IN VITRO* AND IN LABORATORY RESEARCH ANIMALS:  
☐ **Caution.** Contains a new animal drug for investigational use only in laboratory research animals or for tests *in vitro*. Not for use in humans.
2. NEW ANIMAL DRUGS FOR CLINICAL INVESTIGATION IN ANIMALS:  
☒ **Caution.** Contains a new animal drug for use only in investigational animals in clinical trials. Not for use in humans. Edible products of investigational animals are not to be used for food unless authorization has been granted by the U.S. Food and Drug Administration or by the U.S. Department of Agriculture.
3. NEW ANIMAL DRUGS FOR EXPORT IN ANIMALS:  
☐ **Caution.** Contains a new animal drug for use only in investigational clinical trials. Not for use in humans. Edible products from animals used for investigation are not to be used for food in any manner contrary to the requirements of the country in which the clinical trials are to be conducted.

If the drug is intended for food-producing animals, the label must also bear:

☐ No official withdrawal time has been established for this product under the proposed investigational use.

## IV. Sponsor Information

1. SPONSOR'S NAME: AB SCIENCE
2. SPONSOR'S ADDRESS: 3 AVENUE GEORGE V  
75008 PARIS  
FRANCE
3. SPONSOR CONTACT'S SIGNATURE:
4. SPONSOR CONTACT'S NAME: ALAIN MOUSSY
5. SPONSOR CONTACT'S PHONE NUMBER: +33 147 20 23 11
6. SPONSOR CONTACT'S FAX NUMBER: +33 147 20 24 11
7. SPONSOR CONTACT'S E-MAIL ADDRESS: ALAIN.MOUSSY@AB-SCIENCE.COM

## V. Comments

Are there additional comments? ☒ Yes ☐ No

INAD/IFA No.:

DATE:

**NOTE:** IF THE INVESTIGATION IS DISCONTINUED, THE CENTER FOR VETERINARY MEDICINE SHOULD BE NOTIFIED, GIVING THE REASON AND DISPOSITION OF THE DRUG.

## EXHIBIT J

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 7,423,055

Docket No. 71247-0144

Issued: September 9, 2008

To: Ciufolini et al.

For: : 2-(3-AMINOARYL)AMINO-4-  
ARYLTHIAZOLES FOR  
THE TREATMENT OF DISEASES

Assignee: AB Science

APPOINTMENT OF SPECIAL POWER OF ATTORNEY

Commissioner for Patents  
Alexandria, VA 22313-1450

Sir:

**AB SCIENCE**, the undersigned assignee in the above-captioned patent, hereby appoints Conrad J. Clark (Reg. No. 30,340), and Christopher W. Brody (Reg. No. 33,613) as attorneys with full power to make an application for patent term extension for the above-captioned United States Patent No. 7,423,055 and to transact all business in the Patent and Trademark Office in connection with said application for patent term extension.

Please send all correspondence in connection with the patent term extension to:

**Customer No. 22902**  
**CLARK & BRODY**  
1700 Diagonal Road, Suite 510  
Alexandria, VA 22314  
Telephone: 202-835-1111  
Facsimile: 703-504-9415

Respectfully submitted,


Signature:

Printed Name:

Title:

Date:

Telephone No.

  
\_\_\_\_\_  
*Alain noussy*  
\_\_\_\_\_  
*CEO AB Science*  
\_\_\_\_\_  
*Jan 28th 2011*  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_



**COPY**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**In re:** U.S. Patent No. 7,423,055 Attorney Docket No.: 71247-0144

**Issued:** September 9, 2008

**Inventors:** Ciufolini, et al.

**Assignee:** AB SCIENCE

**For:** 2-(3-Aminoaryl)Amino 4-Arylthiazoles For The Treatment Of Diseases

**MAIL STOP PATENT EXTENSION**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**APPLICATION FOR THE EXTENSION OF THE TERM  
OF THE UNITED STATES PATENT NO. 7,423,055  
UNDER 35 U.S.C. § 156**

Sir:

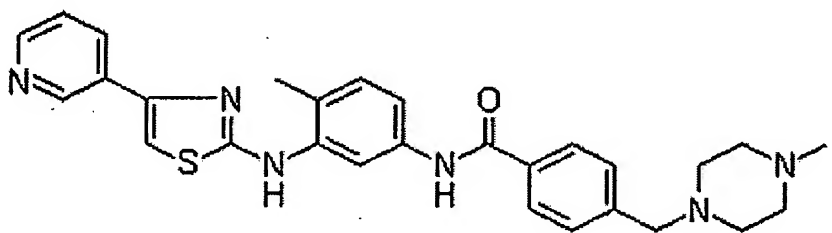
In accordance with 35 U.S.C. § 156 and 37 C.F.R. § 1.740, AB Science, a corporation of France, ("AB Science"), through the undersigned, represents that it is the owner of record of United States Patent No. 7,423,055 ("the '055 patent"), attached hereto as Exhibit A, and hereby requests an extension of the patent term thereof. A copy of the assignment and assignment recordation from the '055 patent, which were recorded on January 12, 2004 at Reel 014872, Frame 0028 confirming that all right, title, and interest resides in AB Science, is attached hereto as Exhibit B.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740. The sections of this application are numbered in a manner corresponding with

the numbering of subparagraphs (1) to (15) of 37 C.F.R. § 1.740(a) and follow the format set forth therein.

***(1) "A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics."***

The approved product is sold under the trade name KINAVET-CA1, the active ingredient of which is masinitib. A chemical name of masinitib is 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-4-yl-thiazol-2-ylamino)-phenyl]-benzamide, and the structure is shown below:



Synonyms for masinitib include AB1010, MM, and KINAVET. The molecular weight of masinitib is 498.67 g/mol, and its empirical formula is C<sub>28</sub>H<sub>30</sub>N<sub>6</sub>OS. (See Product Label, Exhibit C, page 1).

As currently approved, the product sold under the trade name KINAVET-CA1 is indicated for the treatment of recurrent (post-surgery) or nonresectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and/or chemotherapy except corticosteroids in dogs. (See Product Label, Exhibit C, page 1). Currently, the approved product is available in the form of a tablet for oral administration. (See Product Label, Exhibit C, page 1).

***(2) "A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred."***

The product sold under the trade name KINAVET-CA1 (masinitib) was subject to regulatory review for an investigational new animal drug application ("INAD") and a conditional

new animal drug application (“NADA”) under section 571(b) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §§ 360ccc(b) (“FFDCA”). Section 571(b) authorizes the conditional approval of an application pending the full demonstration of effectiveness under section 512(d)(1)(E) (21 U.S.C. § 360b(d)(1)(E)) within 5 years. The Food and Drug Administration (“FDA”) approved the KINAVET-CA1 product (conditional NADA 141-308) under the authority granted by section 571(b) of the FFDCA, 21 U.S.C. § 360ccc(b).

***(3) “An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.”***

The product sold under the trade name KINAVET-CA1 (masinitib) conditionally received permission for commercial marketing or use from the FDA pursuant to section 571(b) of the FFDCA, 21 U.S.C. § 360ccc(b), on December 15, 2010. According to the approval received from the FDA, the application is conditionally approved for one year from December 15, 2010 and is renewable annually for up to four additional one-year terms upon demonstration that Applicant is making sufficient progress toward meeting the approval requirements under section 512(d)(1)(E) of the FFDCA, the quantity of the drug distributed is consistent with the conditionally intended use, and the same drug in the same dosage form for the same intended use has not received approval under Section 512. Copies of the Product Label and FDA conditional approval letter are attached as Exhibits C and D, respectively.

***(4) “In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.”***

The active ingredient in the product sold under the trade name KINAVET-CA1 is masinitib. Masinitib has not been previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act or the Virus-Serum-Toxin Act.

***(5) “A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the last day on which the application could be submitted.”***



This application is being submitted within the sixty days from receipt of the conditional approval under Section 571 of the FFDCA from the FDA. To the extent Section 571 of the FFDCA can serve as a basis for patent term extension, this application is being submitted within the sixty day period permitted for submission pursuant to 37 C.F.R. § 1.720(f), the last day for said submission being February 12, 2011.

***(6) "A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration."***

The complete identification of the patent for which extension is sought is as follows:

Inventors:	Marco Ciufolini, Camille Wermuth, Bruno Gielthen, and Alain Moussy
Patent No.:	7,423,055
Issue Date:	September 9, 2008
Expiration Date:	August 1, 2023

***(7) "A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings."***

A copy of U.S. Patent No. 7,423,055 ("the '055 patent"), for which this extension is sought, is attached hereto as Exhibit A.

***(8) "A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or re-examination certificate issued in the patent."***

A copy of the terminal disclaimer filed and received at the United States Patent and Trademark Office on April 10, 2008, which disclaims the terminal part of the '055 patent extending beyond the expiration of U.S. Patent Application No. 11/779,633, is attached hereto as Exhibit E.

No reexamination certificate for the '055 patent was issued.

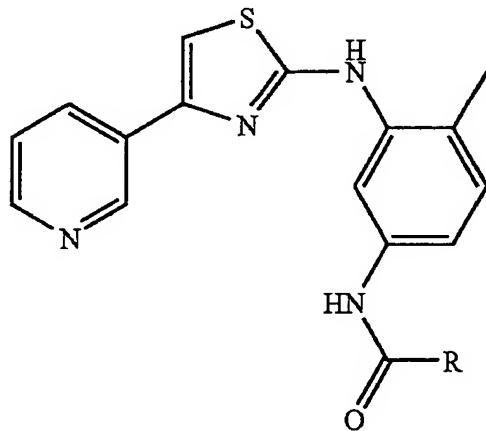
The first maintenance fee payment is not due until March 9, 2012 so no maintenance fee payment receipt is available.

***(9) "A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim"***

*and demonstrates the manner in which at least one such patent claim reads on: (i) The approved product, if the listed claims include any claim to the approved product; (ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and (iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product.”*

The '055 patent claims, *inter alia*, a composition of the approved product, *e.g.* the active ingredient of the product sold under the trade name KINAVET-CA1. More specifically, at least claims 1, 5, 7-10, 13-18, and 20 of the '055 patent read on the approved product. Claims 1, 5, 7-10, 13-18, and 20 are set forth below along with a showing as to how the claims read on the approved product:

**Claim 1.** A compound according to the following formula:

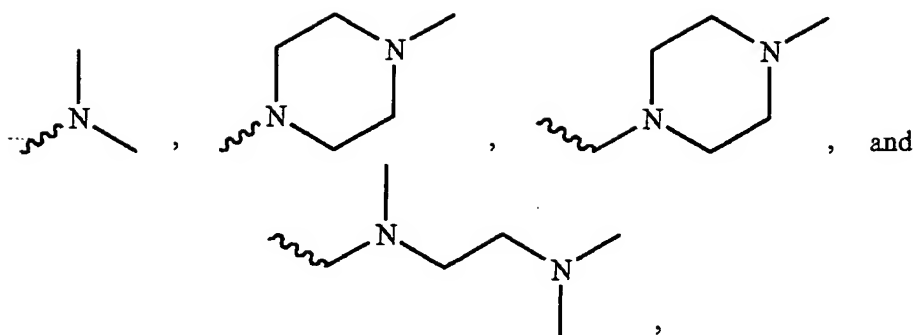


wherein R is:

H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality; or

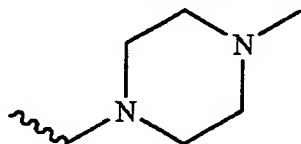
a cycloalkyl, an aryl or heteroaryl group optionally substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

wherein said pendant basic nitrogen functionality is selected from the group consisting of



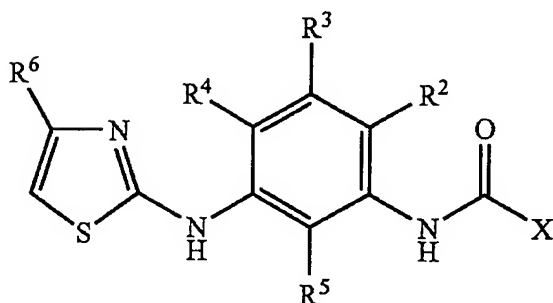
wherein the wavy line corresponds to the point of attachment.

Claim 1 reads on the approved product when  
R=aryl substituted by a pendant basic nitrogen functionality which is

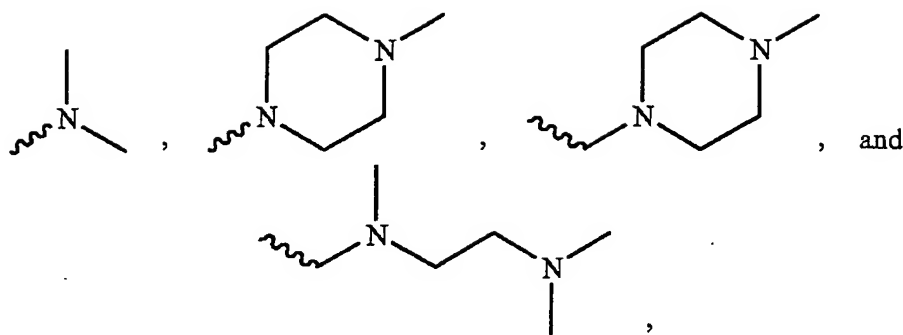


**Claim 5.** A compound according to formula II:

FORMULA II



wherein X is R or NRR' and wherein R and R' are independently chosen from H, an aryl, an heteroaryl, an alkyl and a cycloalkyl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality; an aryl, an heteroaryl, an alkyl and a cycloalkyl group substituted with an aryl, an heteroaryl, an alkyl and a cycloalkyl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality; wherein said pendant basic nitrogen functionality is selected from the group consisting of



wherein the wavy line corresponds to the point of attachment;

$R^2$  is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

$R^3$  is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

$R^4$  is halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

$R^5$  is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

$R^6$  is one of the following:

- (i) an aryl group optionally substituted by one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, or alkoxy;
- (ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear one or more substituents;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl, which may additionally bear one or more substituents.

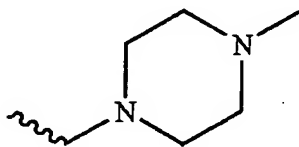
Claim 5 reads on the approved product when

$R^2, R^3, R^5$  = hydrogen

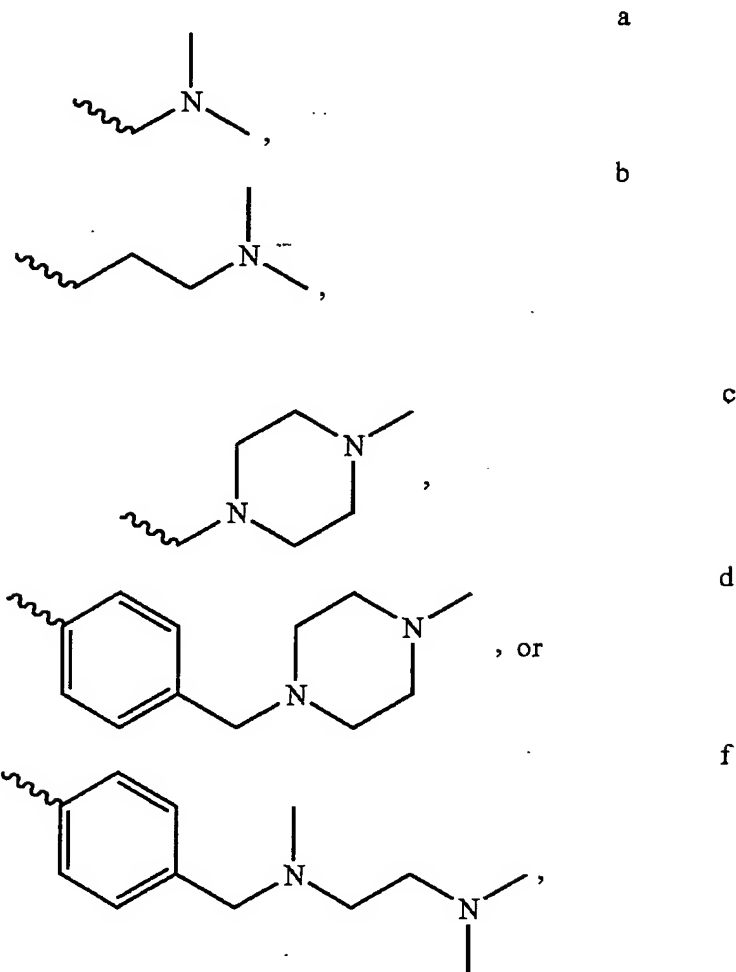
$R^4$  = methyl (alkyl with 1 carbon atom)

$R^6$  = 3-pyridyl group

X = R wherein R is aryl substituted by a pendant basic nitrogen functionality which is



**Claim 7.** A compound according to claim 5, wherein X is selected from the structures (a)-(d) and (f) shown below:



wherein the wavy line corresponds to the point of attachment to core structure of formula II.

Claim 7 reads on the approved product when

X= structure d),

$R^2, R^3, R^5$  =Hydrogen,

$R^4$ = methyl (alkyl with 1 carbon atom) and

$R^6$ = 3-pyridyl group.

**Claim 8.** A compound according to claim 7, wherein X is group (d) and  $R^6$  is a 3-pyridyl group.

Claim 8 reads on the approved product when

$R^2, R^3, R^5$  =hydrogen, and

$R^4$  = methyl (alkyl with 1 carbon atom).

**Claim 9.** A compound according to claim 7, wherein X is group (d) and  $R^4$  is a methyl group.

Claim 9 reads on the approved product when

$R^2, R^3, R^5$  = hydrogen, and

$R^6$  = 3-pyridyl group.

**Claim 10.** A compound according to claim 7, wherein X is group (d) and  $R^2$  and/or  $R^3$  and/or  $R^5$  is H.

Claim 10 reads on the approved product when

$R^2, R^3, R^5$  = hydrogen,

$R^4$  = methyl (alkyl with 1 carbon atom), and

$R^6$  = 3-pyridyl group.

**Claim 13.** The compound of claim S which is: 4-(4-methyl-piperazin-1-yl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 060) or 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-ylthiazol-2-ylamino)-phenyl]-benzamide (example 066).

Claim 13 reads on the approved product since it presents two alternative compounds, the latter one describing a chemical compound 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-4-yl-thiazol-2-ylamino)-phenyl]-benzamide, which encompasses the methanesulfonate-containing active ingredient of the approved product.

**Claim 14.** A compound which is: 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 066).

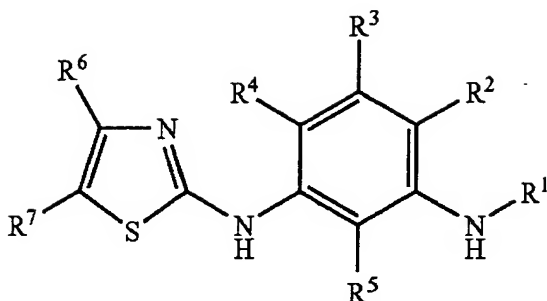
Claim 14 specifically claims the latter alternative of claim 13 and reads on the approved product for the same reason as set forth above for claim 13.

**Claim 15.** A composition comprising a compound of claim 14 and a pharmaceutically acceptable carrier.

Claim 15 reads on the approved product since the approved product, which is covered by claim 14, is in a pharmaceutically acceptable carrier.

**Claim 16.** A compound of formula I:

## FORMULA I



wherein  $R^1$  is:  $-C(O)R$ ,  $-C(O)OR$ , or  $-CO-NRR'$ , wherein  $R$  and  $R'$  are independently selected from the group consisting of hydrogen, aryl, heteroaryl, alkyl, and cycloalkyl, each optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality;

$R^2$  is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

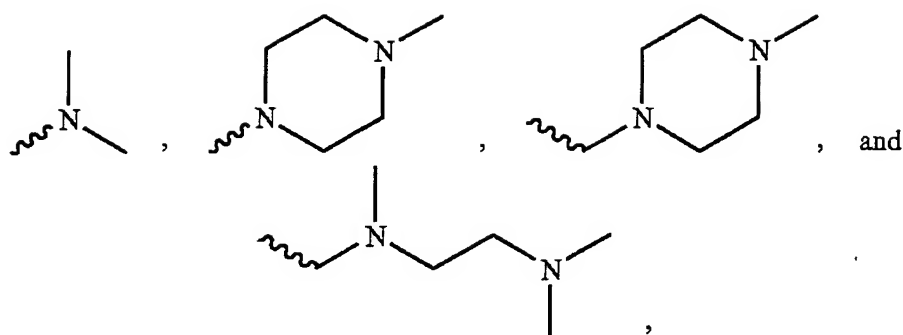
$R^3$  is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

$R^4$  is halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

$R^5$  is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

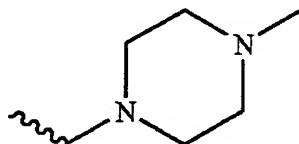
$R^6$  is one of the following: (i) an aryl group such as phenyl optionally substituted by one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, or alkoxy; (ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear one or more substituents; or (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl, which may additionally bear one or more substituents;

and  $R^7$  is one of the following: (i) an aryl group such as phenyl optionally substituted by one or more substituents; (ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear one or more substituents; (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl, which may additionally bear one or more substituents; or (iv) H, a halogen selected from I, F, Cl or Br;  $NH_2$ ,  $NO_2$  and  $SO_2-R''$ , wherein  $R''$  is a linear or branched alkyl group optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality; wherein said pendant basic nitrogen functionality is selected from the group consisting of



wherein the wavy line corresponds to the point of attachment.

Claim 16 reads on the approved product when  
 $R^1 = -C(O)R$  wherein R is aryl substituted by a pendant basic nitrogen functionality which is



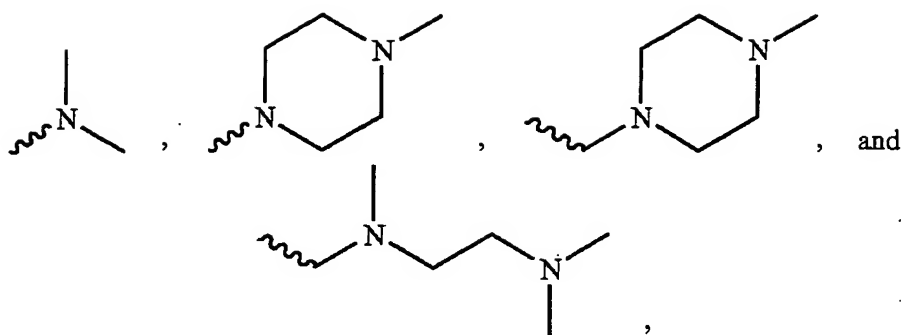
$R^2, R^3, R^5$  = hydrogen,  
 $R^4$  = methyl (alkyl with 1 carbon atom), and  
 $R^6$  = heteroaryl (3-pyridyl group).

**Claim 17.** A composition comprising a compound of claim 16 in a pharmaceutically acceptable carrier.

Claim 17 reads on the approved product since the approved product, which is covered by claim 16, is in a pharmaceutically acceptable carrier.

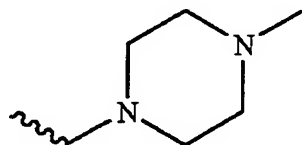
**Claim 18.** A compound according to claim 16, wherein  $R^1$  is  $C(O)R$ , wherein R is independently selected from the group consisting of hydrogen, aryl, heteroaryl, alkyl, and cycloalkyl, each optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality; wherein said pendant basic nitrogen functionality is 60 selected from selected from the group consisting of





wherein the wavy line corresponds to the point of attachment.

Claim 18 reads on the approved product when  
 $\text{R1}$  (not  $\text{R}'$ ) is  $-\text{C}(\text{O})\text{R}$  wherein  $\text{R}$  is aryl substituted by a pendant basic nitrogen functionality which is



**Claim 20.** A pharmaceutical composition comprising a compound according to claim 18 and a pharmaceutically acceptable carrier.

Claim 20 reads on the approved product since the approved product, which is covered by claim 18, is in a pharmaceutically acceptable carrier.

***(10) “A statement, beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:***

***...(ii) For a patent claiming a new animal drug:***

***(A) The date a major health or environmental test on the drug was initiated, and any available substantiation of that date, or the date of an exemption under subsection (j) of Section 512 of the Federal Food, Drug, and Cosmetic Act became effective for such animal drug;***

***(B) The date on which a new animal drug application (NADA) was initially submitted and the NADA number; and***

***(C) The date on which the NADA was approved”.***

The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period for the product sold under the trade name KINAVET-CA1 are as follows:

(a) A letter dated March 11, 2004 from the FDA administratively assigned Investigational new animal drug (“INAD”) application number 011206. (Attached as Exhibit H). A Notice of Claimed Investigational Exemption (NCIE) for a New Animal Drug was filed with the FDA on February 1, 2005. (Attached as Exhibit I). In addition, studies relevant to the conditional approval for the product sold under the trade name KINAVET-CA1 were conducted as early as April 2003, e.g., 4-Week Toxicity Study described in Section III, B of the Freedom of Information Summary attached in Exhibit G. Accordingly, Applicant believes that the date a major health or environmental test on the drug was initiated or the date of an exemption under subsection (j) of section 512 of the FFDCA is at least on or around February 1, 2005, if not earlier.

Although Applicant may be entitled to an earlier date under 37 C.F.R. § 1.740(a)(10)(ii)(A), for the purposes of calculating the patent term extension of the ‘055 patent based on the conditional approval of conditional NADA application 141-307 under Section 571(b) herein, Applicant will use February 1, 2005. Applicant notes that this date is well before September 9, 2008, the issue date of the ‘055 patent, and that 37 C.F.R. §1.778(d)(1)(i) requires subtraction from the patent term extension calculations the number of days on and before the date the patent issued. (b) The conditional new animal drug application under Section 571 was submitted on July 9, 2010 for conditional approval, and was assigned conditional NADA

number 141-308.

(c) Conditional NADA number 141-308 was conditionally approved by the FDA on December 15, 2010 (Exhibit D).

(d) According to the approval letter received from the FDA, the conditional application is conditionally approved for one year, which will expire on December 15, 2011. However, the conditional application is renewable annually for up to four additional one-year terms upon filing a request to renew this application within 90 days from the end of the one-year period demonstrating that Applicant is making sufficient progress toward meeting the approval requirements under section 512(d)(1)(E) of the FFDCa, the quantity of the drug distributed is consistent with the conditionally intended use, and the same drug in the same dosage form for the same intended use has not received approval under Section 512.

***(11) "A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities."***

A chronology of selected regulatory activities is attached hereto as Exhibit F to briefly describe certain activities undertaken with respect to the approval of the product under the trade name KINAVET-CA1 during the applicable regulatory review period and the dates applicable to such activities. Also attached as Exhibit G is the Freedom of Information Summary, which details the various tests conducted in connection with the regulatory review period.

***(12) “A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined.”***

Applicant respectfully submits that 35 U.S.C. § 156 and the associated regulations do not clearly address whether a product reviewed under Section 571 of the FFDCA would be eligible for patent term extension. Applicant is unaware of any prior decisions by the USPTO or the FDA addressing this particular issue and believes that this is one of first impression for these regulatory agencies. Pursuant to § 156(d)(1), a patent term application “may only be submitted within the sixty-day period beginning on the date the product received permission under the provision of law under which the applicable regulatory review period occurred for commercial marketing or use.” Therefore, Applicant submits this application within 60 days of receiving the FDA’s conditional approval of KINAVET-CA1 (conditional NADA 141-308) to request administrative review whether conditional approval of an animal drug under Section 571 of the FFDCA can serve as a basis for patent term extension. If so, Applicant respectfully requests for an extension of **493 days**, the calculation of which is further described below. Should the delays based on regulatory review under Section 571 not be eligible for patent term extension under 35 U.S.C. § 156(g), then Applicant respectfully submits that a subsequent regulatory approval of KINAVET-CA1 under Section 512(b) should be considered as “the first permitted commercial marketing or use of the product” as required by § 156(a)(5)(A) and reserves the right to file a subsequent patent term extension application based on subsequent express approval under Section 512(b).

The conditional NADA application under Section 571(a) of the FFDCA is an alternative regulatory process to authorize the distribution and commercial marketing of new animal drugs “intended for a minor use or a minor species,” instead of the so-called “traditional” NADA under Section 512 of the FFDCA. Pursuant to the statute, conditional NADA applications under Section 571(a) “must comply in all respects with the provisions of section 512 of this Act” except for certain statutorily exempt sections. In particular, the statute states that “[n]ew animal drugs are subject to application of the same safety standards that would be applied to such drugs under section 512(d) (including, for antimicrobial new animal drugs, with respect to antimicrobial resistance).” 21 U.S.C. §360ccc(a)(1). Consistent with the language of the statute, and the FDA’s guidelines regarding minor use and minor species animal drug applications, the

conditional approval issued under section 571(b) of the Federal Food, Drug, and Cosmetic “provides for animal drug marketing after all safety and manufacturing components of a new animal drug approval have met the standards of section 512 of the act (for the effectiveness component, a reasonable expectation of effectiveness must be established, after which sponsors have up to 5 years to complete the demonstration of effectiveness by the standards of section 512 of the act and achieve a full approval).” 70 Fed. Reg. 56394 (Sept. 27, 2005).

In addition to incorporating the substantive requirements of Section 512 of the FFDCA, the regulatory approval process under Section 571 is closely integrated with the statutory process under Section 512. Most notably, Section 512(b)(3) specifically incorporates a process for “[a]ny person intending to file an application under paragraph (1), section 571” to obtain one or more conferences with the FDA prior to submission of the conditional NADA. Applicant also notes that Section 512 refers to a conditional approval of an application filed pursuant to Section 571 as one possible route for an animal drug to be reviewed and deemed safe by the FDA. See 21 USC § 360b(a)(1)(B) and (a)(2)(A)(ii). Section 512(f), (g), (i), (l)(1) and (p)(1) provide identical review and record keeping processes for both Section 512 and Section 571 applications including: process for addressing decisions refusing, withdrawing or suspending approval; process for granting an order; process for publication in the Federal Register; requirements for record keeping and requirements for public access to safety and effective data.

In light of the integrated approval provisions of Sections 512 and 571 and the specific procedure established in Section 512(b) for initiating Section 571 applications, Applicant respectfully submits that the statutory language does not clearly address whether a product reviewed under Section 571 of the FFDCA would be eligible for patent term extension. Should Section 571 of the FFDCA be construed to be part of a regulatory regime that is eligible for patent term extension under 35 U.S.C. §156(g) (for example, as a type of Section 512(b) application), Applicant believes it appropriate to refer to the dates of submission and approval of NADA 141-308 below.

To the extent Section 571 of the FFDCA can serve as a basis for patent term extension, Applicant respectfully submits that that the '055 patent should be eligible for an extension and estimates the extension to be **493 days**, the calculation of which is described below. Applicant

notes that the calculations provided below reflect the conditional approval of conditional NADA 141-308 on December 15, 2010. Should the delays based on regulatory review under Section 571 not be eligible for patent term extension under 35 U.S.C. §156(g), Applicants respectfully submit that the calculations provided in Sections A, B and C are not applicable and reserve the right to submit alternative calculations based on a subsequent Section 512(b) regulatory approval.

A. Eligibility:

(a) Pursuant to 35 U.S.C. § 156(a), the '055 patent claims a composition of the active ingredient;

(b) Pursuant to 35 U.S.C. § 156(a)(1), the term of the '055 patent has not expired before submission of this application for extension;

(c) Pursuant to 35 U.S.C. § 156(a)(2), the term of the '055 patent has never been extended;

(d) Pursuant to 35 U.S.C. § 156(a)(3), the application for extension is submitted by the owners of record of the '055 patent;

(e) To the extent Section 571 of the FFDCA can serve as a basis for patent term extension, Applicant respectfully submits that the approved product, sold under the trade name KINAVET-CA1, has been subject to a regulatory review period before its commercial marketing or use pursuant to 35 U.S.C. § 156(a)(4);

(f) To the extent Section 571 of the FFDCA can serve as a basis for patent term extension, Applicant respectfully submits that the permission for the commercial marketing or use of the product sold under the trade name KINAVET-CA1 after the regulatory review period is the first permitted commercial marketing or use of this product pursuant to 35 U.S.C. § 156(a)(5).

(g) Pursuant to 35 U.S.C. § 156(c)(4), no other patent has been extended for the same regulatory review period for the approved product sold under the trade name

KINAVET-CA1.

B. Regulatory Review Period:

(a) The period from **February 1, 2005** (as discussed above, the date a major health or environmental test on the drug was initiated or the date of an exemption under subsection (j) of section 512 of the FFDCA is at least on or around February 1, 2005, if not earlier) to July 9, 2010 (the date the conditional NADA under Section 571 was initially submitted) is 1984 days. To the extent Section 571 of the FFDCA can serve as a basis for patent term extension, Applicant respectfully submits that the “Testing Phase” should be 1984 days pursuant to 37 C.F.R. § 1.778(c)(1).

(b) Pursuant to 37 C.F.R. § 1.778(c)(2), the period from July 9, 2010 (the date the conditional NADA under Section 571 was initially submitted) to December 15, 2010 (the date of NADA conditional approval) is 159 days. To the extent Section 571 of the FFDCA can serve as a basis for patent term extension, Applicant respectfully submits that the “Approval Phase” should be 159 days pursuant to 37 C.F.R. § 1.778(c)(2).

C. Extended Patent Term:

(a) The number of days in the regulatory review period described in section B above which were on and before September 9, 2008, the date on which the '055 patent issued, is 1316 days. Accordingly, 1316 days are subtracted from the regulatory review pursuant to 37 C.F.R. § 1.778(d)(1)(i).

(b) As demonstrated in Exhibit F, the Applicant acted with due diligence during the regulatory review period. Accordingly, zero (0) days are subtracted from the regulatory review period pursuant to 37 C.F.R. § 1.778(d)(1)(ii).

(c) To the extent Section 571 of the FFDCA can serve as a basis for patent term extension, one half of the number of days remaining in the Testing Phase (as calculated in Section B above) after the consideration of potential reductions pursuant to paragraphs (a) and (b) above is 334 days. Accordingly, 334 days are subtracted from the regulatory review period



pursuant to 37 C.F.R. § 1.778(d)(1)(iii). Applicants respectfully submit that after the above adjustments, the total remaining Testing Phase and Approval Phase is 493 days (334 days plus 159 days), should the delays based on regulatory review under Section 571 be eligible for patent term extension under 35 U.S.C. § 156(g).

(d) The period remaining in the term of the patent (set to expire August 1, 2023) measured from the date of conditional approval of the product sold under the trade name KINAVET-CA1 (December 15, 2010) (4612 days) when added to the period of extension (493 days) is 5105 days, which is less than fourteen (14) years. Accordingly, the fourteen (14) year limitation set forth in 37 C.F.R. § 1.775(d)(2)-(4) does not operate to reduce the regulatory review period.

(e) The period of extension (493 days) is less than five (5) years. Accordingly, the five (5) year limitation set forth in 37 C.F.R. § 1.778(d)(5)(i)(ii) does not operate to further reduce the regulatory review period.

***(13) "A statement that applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to any determination of entitlement to the extension sought."***

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought pursuant to 37 C.F.R. § 1.765.

As discussed above, Applicants respectfully submits that 35 U.S.C. § 156 and the associated regulations do not clearly address whether a product conditionally approved under Section 571 of the FFDCA would be eligible for patent term extension. Applicant is unaware of any prior decisions by the USPTO or the FDA addressing this particular issue and believes that this is one of first impression by for these regulatory agencies. Therefore, Applicant submits this application to request administrative determination of whether conditional approval of an animal drug under Section 571 of the FFDCA can serve as a basis for patent term extension.

***(14) "The prescribed fee for receiving and acting upon the application for extension."***

The prescribed fee for receiving and acting upon this application is believed to be \$1,120.00 pursuant to 37 C.F.R. § 1.20(j)(1). A fee transmittal letter is attached to pay the application fee. The Commissioner is authorized to charge this fee and any additional required fees, or credit any overpayment, to Deposit Account No. 50-1088.

***(15) "The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed."***

Please direct all inquiries and correspondence relating to this application to:

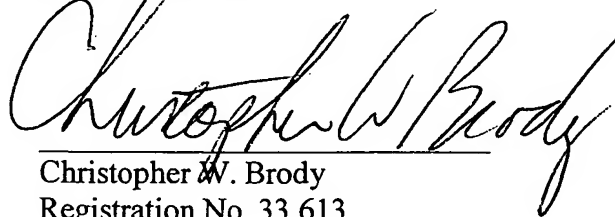
Christopher W. Brody  
Clark & Brody  
1700 Diagonal Road, Suite 510  
Alexandria, VA 22314  
Tel:(202)835-1753  
Fax (703) 504-9415

A power of attorney (Exhibit J) is also enclosed so that the record will reflect correspondence should be addressed to Customer No. 22902.

***(16) "The application under this section must be accompanied by two additional copies of such application (for a total of three copies)."***

This Application is accompanied by two additional copies of such application for a total of three copies as required by 37 C.F.R. § 1.740(b). The undersigned attorney for Applicants hereby states that these copies are accurate and true duplicates of the original.

Respectfully submitted,  
CLARK & BRODY



Christopher W. Brody  
Registration No. 33,613

***Customer No. 22902***

1700 Diagonal Road, Suite 510  
Alexandria, VA 22314  
Telephone: 202-835-1111  
Facsimile: 703-504-9415  
Docket No.: 71247-0144  
Date: February 11, 2011

**PROPRIETARY MATERIAL NOT OPEN TO PUBLIC**  
**DO NOT SCAN**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**In re:** U.S. Patent No. 7,423,055 Attorney Docket No.: 71247-0144  
**Issued:** September 9, 2008  
**Inventors:** Ciufolini, et al.  
**Assignee:** AB SCIENCE  
**For:** 2-(3-Aminoaryl)Amino 4-Arylthiazoles For The Treatment Of Diseases

**MAIL STOP PATENT EXTENSION**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**FEE TRANSMITTAL LETTER**  
**FOR AN APPLICATION FOR EXTENSION UNDER 35 U.S.C. § 156**

Sir:

Transmitted herewith is an Application for Extension of Patent Term Under 35 U.S.C. § 156 for U.S. Patent No. 7,423,055 accompanied by two additional copies. The undersigned attorney for Applicants hereby state that these copies are certified to be duplicates of the original. Each copy contains the following exhibits:

Exhibit A	U.S. Patent No. 7,423,055
Exhibit B	Assignment Recordation & Assignment
Exhibit C	Approved Product Labels
Exhibit D	FDA Approval Letter
Exhibit E	Terminal Disclaimer
Exhibit F	Compendium of Certain Regulatory Activities in connection with the product sold under the trade name KINAVET-CA1 INAD and NADA (Marked as <b>PROPRIETARY MATERIAL NOT OPEN TO PUBLIC</b> in accordance with MPEP §§2760 and 724.02)
Exhibit G	Freedom of Information Summary for KINAVET-CA1
Exhibit H	Letter dated March 11, 2004 from the FDA administratively assigning INAD No. 011206
Exhibit I	Notice of Claimed Investigational Exemption (NCIE) for a New Animal Drug filed with the FDA on February 1, 2005

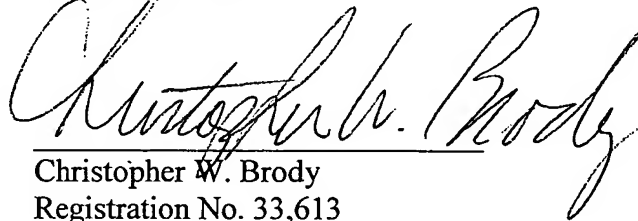
**PROPRIETARY MATERIAL NOT OPEN TO PUBLIC**  
**DO NOT SCAN**

Exhibit J      Power of Attorney

Applicant respectfully request that the Exhibit F provided herewith be treated as PROPRIETARY information and not be made public as part of the patent file in accordance with MPEP §2760.

Please charge Deposit Account No. 50-1088 the fee of \$1,120.00 for the application fee. The Director is hereby authorized to charge any additional fees, which may be required, or credit any overpayment to Deposit Account No. 50-1088.

Respectfully submitted,  
CLARK & BRODY



Christopher W. Brody  
Registration No. 33,613

***Customer No. 22902***

1700 Diagonal Road, Suite 510  
Alexandria, VA 22314  
Telephone: 202-835-1111  
Facsimile: 703-504-9415  
Docket No.: 71247-0144  
Date: February 11, 2011

# EXHIBIT A



US007423055B2

(12) **United States Patent**  
**Ciufolini et al.**

(10) **Patent No.:** **US 7,423,055 B2**  
(45) **Date of Patent:** **\*Sep. 9, 2008**

(54) **2-(3-AMINOARYL)AMINO-4-ARYL-THIAZOLES  
FOR THE TREATMENT OF DISEASES**

(75) **Inventors:** **Marco Ciufolini, Lyons (FR); Camille  
Wermuth, Strasbourg (FR); Bruno  
Gielthen, Illkirch (FR); Alain Moussy,  
Paris (FR)**

(73) **Assignee:** **AB Science, Paris (FR)**

(\*) **Notice:** Subject to any disclaimer, the term of this  
patent is extended or adjusted under 35  
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-  
claimer.

(21) **Appl. No.:** **10/632,101**

(22) **Filed:** **Aug. 1, 2003**

(65) **Prior Publication Data**

US 2004/0110810 A1 Jun. 10, 2004

**Related U.S. Application Data**

(60) **Provisional application No. 60/400,064, filed on Aug.  
2, 2002.**

(51) **Int. Cl.**

**A61K 31/44** (2006.01)  
**C07D 417/04** (2006.01)  
**C07D 417/14** (2006.01)

(52) **U.S. Cl.** ..... **514/342; 514/370; 546/270.4;  
548/194; 544/364**

(58) **Field of Classification Search** ..... **548/190,  
548/194; 546/270.4; 514/342, 370**  
See application file for complete search history.

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

3,192,225 A 6/1965 Spivack et al.

3,201,409 A \* 8/1965 Dexter et al. .... 548/193  
3,467,666 A \* 9/1969 Dexter et al. .... 548/193  
5,521,184 A 5/1996 Zimmermann  
6,291,514 B1 \* 9/2001 Illig et al. .... 514/447  
2001/0044545 A1 \* 11/2001 Dhanoa et al. .... 548/190  
2003/0158199 A1 \* 8/2003 Stieber et al. .... 514/242

**FOREIGN PATENT DOCUMENTS**

WO WO-96/01825 A1 \* 1/1996  
WO WO 99/03854 A 1/1999  
WO WO 00/33842 A 5/2000  
WO WO 00/75120 A 12/2000  
WO WO 01/64200 A 9/2001  
WO WO 01/64674 A 9/2001  
WO WO 02/080925 A 10/2002  
WO WO 03/062215 A 7/2003

**OTHER PUBLICATIONS**

Golub et al., *Science*, vol. 286, Oct. 15, 1999, pp. 531-537.\*  
Schantl et al., *Synthetic Communications* (1998), 28(8), pp. 1451-  
1462.\*

\* cited by examiner

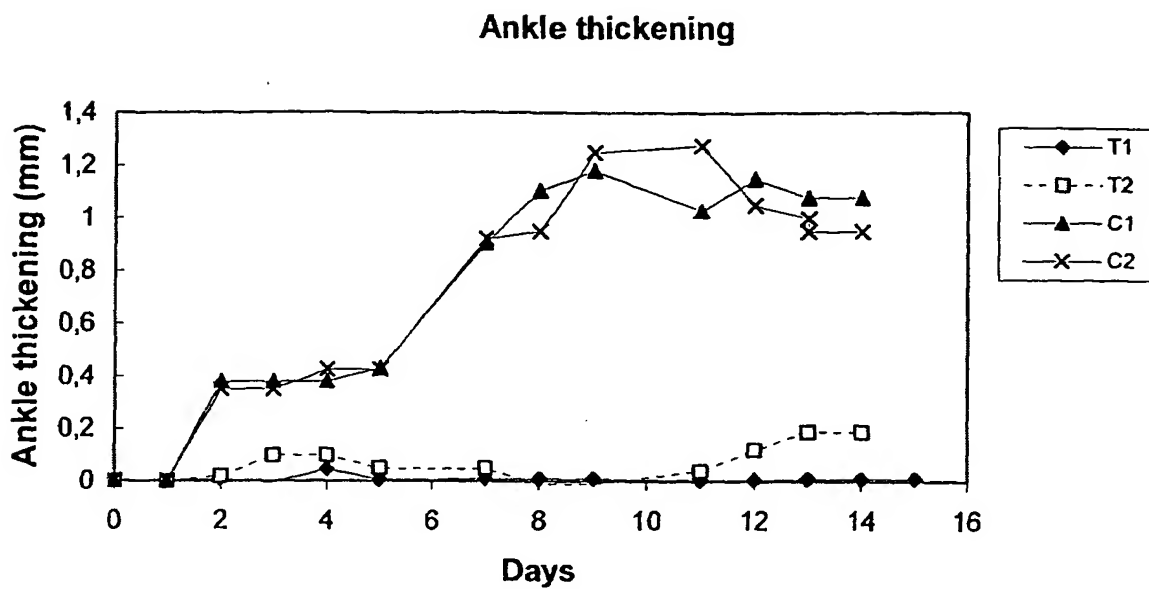
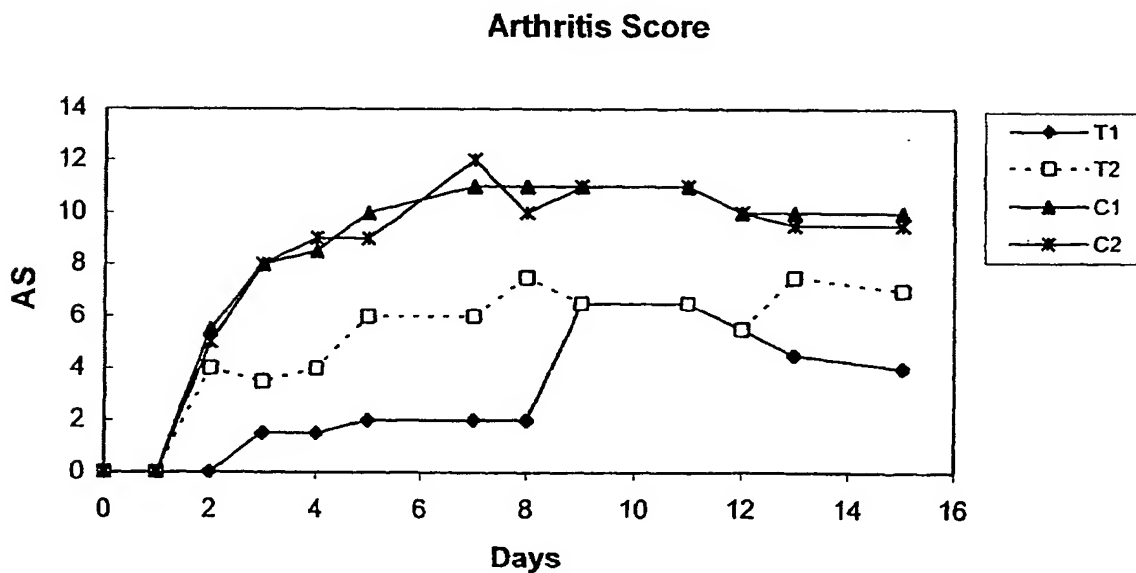
*Primary Examiner*—Laura L. Stockton

(74) *Attorney, Agent, or Firm*—Foley & Lardner

(57) **ABSTRACT**

The present invention relates to novel compounds selected  
from 2-(3-aminoaryl)amino-4-aryl-thiazoles that selectively  
modulate, regulate, and/or inhibit signal transduction medi-  
ated by certain native and/or mutant tyrosine kinases impli-  
cated in a variety of human and animal diseases such as cell  
proliferative, metabolic, allergic, and degenerative disorders.  
More particularly, these compounds are potent and selective  
c-kit inhibitors.

**30 Claims, 2 Drawing Sheets**

**FIGURE 1****FIGURE 2**

## Ankle thickening

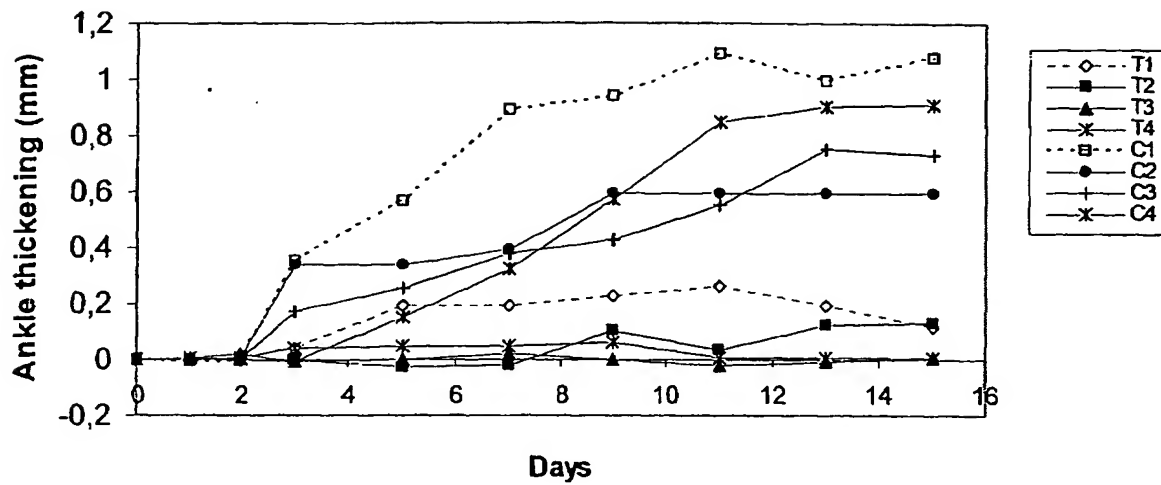


FIGURE 3

## AS

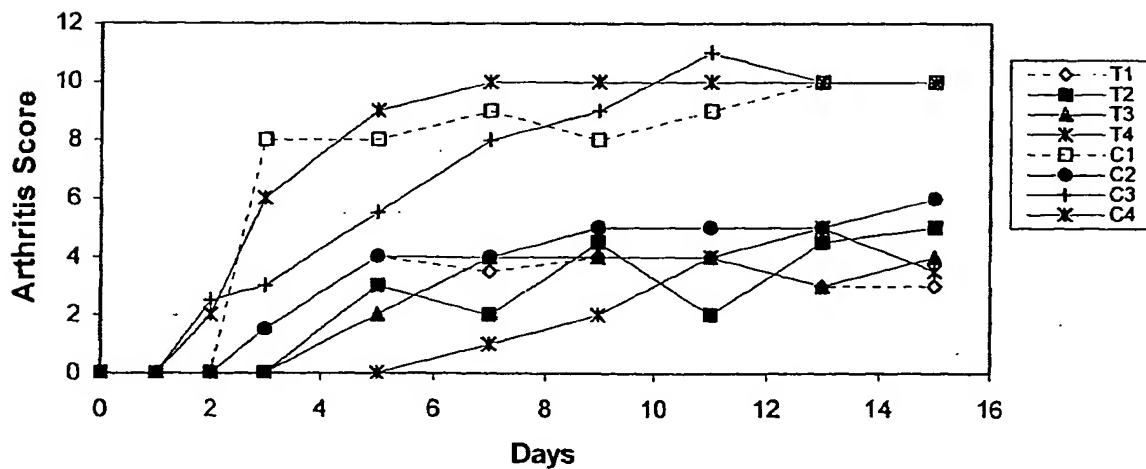


FIGURE 4



## 2-(3-AMINOARYL)AMINO-4-ARYL-THIAZOLES FOR THE TREATMENT OF DISEASES

### BACKGROUND OF THE INVENTION

The present invention relates to novel compounds selected from 2-(3-aminoaryl)amino-4-aryl-thiazoles that selectively modulate, regulate, and/or inhibit signal transduction mediated by certain native and/or mutant tyrosine kinases implicated in a variety of human and animal diseases such as cell proliferative, metabolic, allergic, and degenerative disorders. More particularly, these compounds are potent and selective c-kit inhibitors.

Tyrosine kinases are receptor type or non-receptor type proteins, which transfer the terminal phosphate of ATP to tyrosine residues of proteins thereby activating or inactivating signal transduction pathways. These proteins are known to be involved in many cellular mechanisms, which in case of disruption, lead to disorders such as abnormal cell proliferation and migration as well as inflammation.

As of today, there are about 58 known receptor tyrosine kinases. Other tyrosine kinases are the well-known VEGF receptors (Kim et al., Nature 362, pp. 841-844, 1993), PDGF receptors, c-kit and the FLK family. These receptors can transmit signals to other tyrosine kinases including Src, Raf, Frk, Btk, Csk, Abl, Fes/Fps, Fak, Jak, Ack, etc.

Among tyrosine kinase receptors, c-kit is of special interest. Indeed, c-kit is a key receptor activating mast cells, which have proved to be directly or indirectly implicated in numerous pathologies for which the Applicant filed WO 03/004007, WO 03/004006, WO 03/003006, WO 03/003004, WO 03/002114, WO 03/002109, WO 03/002108, WO 03/002107, WO 03/002106, WO 03/002105, WO 03/039550, WO 03/035050, WO 03/035049, U.S. 60/359,652 and U.S. 60/359,651.

It was found that mast cells present in tissues of patients are implicated in or contribute to the genesis of diseases such as autoimmune diseases (rheumatoid arthritis, inflammatory bowel diseases (IBD)) allergic diseases, tumor angiogenesis, inflammatory diseases, and interstitial cystitis. In these diseases, it has been shown that mast cells participate in the destruction of tissues by releasing a cocktail of different proteases and mediators such as histamine, neutral proteases, lipid-derived mediators (prostaglandins, thromboxanes and leucotrienes), and various cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, TNF- $\alpha$ , GM-CSF, MIP-1a, MIP-1b, MIP-2 and IFN- $\gamma$ ).

The c-kit receptor also can be constitutively activated by mutations leading to abnormal cell proliferation and development of diseases such as mastocytosis and various cancers.

For this reason, it has been proposed to target c-kit to deplete the mast cells responsible for these disorders.

The main objective underlying the present invention is therefore to find potent and selective compounds capable of inhibiting wild type and/or mutated c-kit.

Many different compounds have been described as tyrosine kinase inhibitors, for example, bis monocyclic, bicyclic or heterocyclic aryl compounds (WO 92/20642), vinylene-azaindole derivatives (WO 94/14808) and 1-cyclopropyl-4-pyridyl-quinolones (U.S. Pat. No. 5,330,992), styryl compounds (U.S. Pat. No. 5,217,999), styryl-substituted pyridyl compounds (U.S. Pat. No. 5,302,606), seleninoides and selenides (WO 94/03427), tricyclic polyhydroxylic compounds (WO 92/21660) and benzylphosphonic acid compounds (WO 91/15495), pyrimidine derivatives (U.S. Pat. No. 5,521,184 and WO 99/03854), indolinone derivatives and pyrrole-substituted indolinones (U.S. Pat. No.

5,792,783, EP 934 931, U.S. Pat. No. 5,834,504, U.S. Pat. No. 5,883,116, U.S. Pat. No. 5,883,113, U.S. Pat. No. 5,886,020, WO 96/40116 and WO 00/38519), as well as bis monocyclic, bicyclic aryl and heteroaryl compounds (EP 584 222, U.S. Pat. No. 5,656,643 and WO 92/20642), quinazoline derivatives (EP 602 851, EP 520 722, U.S. Pat. No. 3,772,295 and U.S. Pat. No. 4,343,940) and aryl and heteroaryl quinazoline (U.S. Pat. No. 5,721,237, U.S. Pat. No. 5,714,493, U.S. Pat. No. 5,710,158 and WO 95/15758).

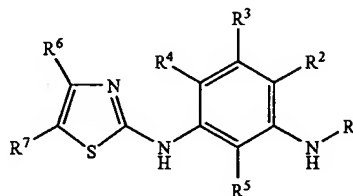
However, none of these compounds have been described as potent and selective inhibitors of c-kit or of the c-kit pathway.

In connection with the present invention, we have found that compounds corresponding to the 2-(3-aminoaryl)amino-4-aryl-thiazoles are potent and selective inhibitors of c-kit or c-kit pathway. These compounds are good candidates for treating diseases such as autoimmune diseases, inflammatory diseases, cancer and mastocytosis.

### BRIEF SUMMARY OF THE INVENTION

Therefore, the present invention relates to compounds belonging to the 2-(3-aminoaryl)amino-4-aryl-thiazoles. These compounds are capable of selectively inhibiting signal transduction involving the tyrosine phosphokinase c-kit and mutant forms thereof. In a first embodiment, the invention is aimed at compounds of formula I, which may represent either free base forms of the substances or pharmaceutically acceptable salts thereof:

FORMULA I



and wherein R<sup>1</sup> is:

- a) a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;
  - b) an aryl or heteroaryl group optionally substituted by an alkyl or aryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;
  - c) a —CO—NH—R, —CO—R, —CO—OR or a —CO—NRR' group, wherein R and R' are independently chosen from H or an aryl, heteroaryl, alkyl and cycloalkyl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;
- R<sup>2</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;
- R<sup>3</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;
- R<sup>4</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;
- R<sup>5</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

3

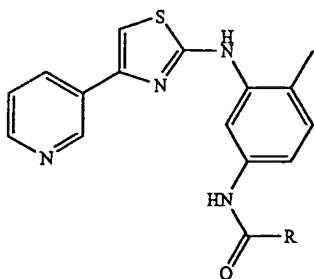
R<sup>6</sup> is one of the following:

- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy,
- iv) H, a halogen selected from 1, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>—R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; and R<sup>7</sup> is one of the following:
  - (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
  - (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
  - (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.
- iv) H, a halogen selected from 1, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>—R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

#### DETAILED DESCRIPTION OF INVENTION

The present invention provides compounds belonging to the 2-3-(amino)aryl-amino-4-aryl-thiazoles, such as those described above with reference to Formula I. These compounds are capable of selectively inhibiting signal transduction involving the tyrosine phosphokinase c-kit and mutant forms thereof.

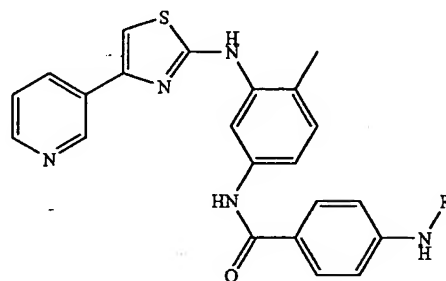
In another preferred embodiment, when R<sup>1</sup> has the meaning depicted in c) above, the invention is directed to compounds of the following formula:



4

wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality.

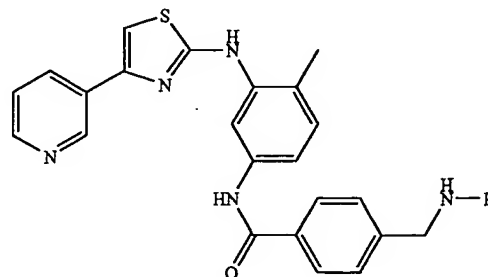
Among the particular compounds in which R1 has the meaning as depicted in c) above, the invention is directed to amide-aniline compounds of the following formula:



wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality; or a a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality;

a —SO<sub>2</sub>—R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality; or a —CO—R or a —CO—NRR' group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

Among the particular compounds in which R1 has the meaning as depicted in c) above, the invention is directed to amide-benzylamine compounds of the following formula:



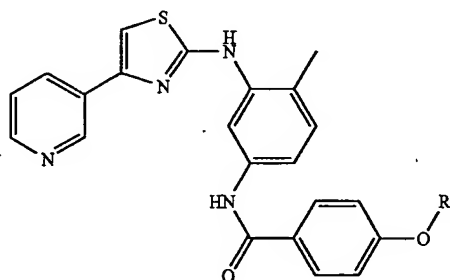
wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing

5

from 1 to 10 carbon atoms optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or an alkyl, cycloalkyl, aryl or heteroaryl group substituted by a alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a —SO<sub>2</sub>—R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a —CO—R or a —CO—NRR' group, wherein R and R' are independently chosen from H or an aryl heteroaryl, alkyl and cycloalkyl group optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality.

Among the particular compounds in which R1 has the meaning as depicted in c) above, the invention is directed to amide-phenol compounds of the following formula:



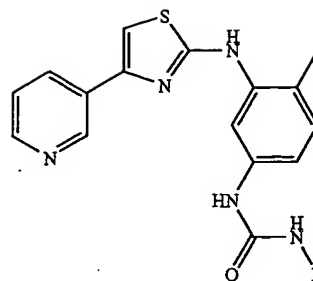
wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

a cycloalkyl, aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality; or an alkyl, cycloalkyl, aryl or heteroaryl group substituted by a alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality;

a —SO<sub>2</sub>—R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality; or a —CO—R or a —CO—NRR' group, wherein R and R' are independently chosen from H or an aryl, heteroaryl, alkyl and cycloalkyl group optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality.

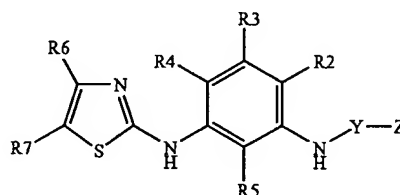
Among the particular compounds in which R1 has the meaning as depicted in c) above, the invention is directed to urea compounds of the following formula:

6



wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

Among the particular compounds in which R1 has the meaning as depicted in a) and b) above, the invention is directed to N-Aminoalkyl-N'-thiazol-2-yl-benzene-1,3-diamine compounds of the following formula:



wherein Y is a linear or branched alkyl group containing from 1 to 10 carbon atoms;

wherein Z represents an aryl or heteroaryl group, optionally substituted at one or more ring position with any permutation of the following groups:

a halogen such as F, Cl, Br, I;

a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

an O—R, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom,

an NRaRb, where Ra and Rb represents a hydrogen, or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality or a cycle; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality:

a COOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

CONRaRb, where Ra and Rb are a hydrogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

an NHCOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

8

an NHCONRaRb, where Ra and Rb are a hydrogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

an  $\text{OSO}_2\text{R}$ , where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

an  $\text{NRaOSO}_2\text{Rb}$ , where Ra and Rb are a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; Ra can also be a hydrogen; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

R<sup>2</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>3</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>4</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>5</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

$R^6$  is one of the following:

60 (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

(ii) a heteroaryl group such as a 2,3- or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.

iv) H, a halogen selected from 1, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; and R<sup>7</sup> is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

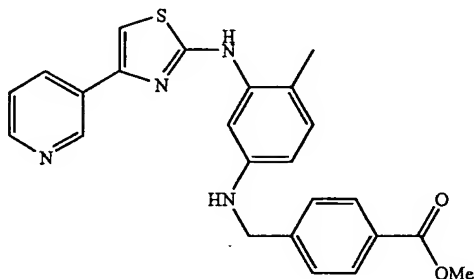
(ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.

iv) H, an halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

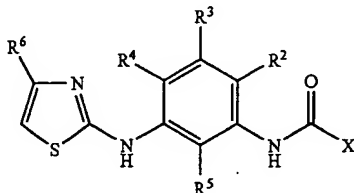
An example of preferred compounds of the above formula is depicted below:

001: 4-{{[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylamino]-methyl}-benzoic acid methyl ester



Among the compounds of formula I, the invention is particularly embodied by the compounds of the following formula II:

FORMULA II



wherein X is R or NRR' and wherein R and R' are independently chosen from H, an aryl, a heteroaryl, an alkyl, or a cycloalkyl group optionally substituted with at least one heteroatom, such as for example a halogen chosen from F, I, Cl and Br and optionally bearing a pendant basic nitrogen functionality; or an aryl, a heteroaryl, an alkyl or a cycloalkyl group substituted with an aryl, a heteroaryl, an alkyl or a cycloalkyl group optionally substituted with at least one heteroatom, such as for example a halogen chosen from F, I, Cl and Br and optionally bearing a pendant basic nitrogen functionality,

R<sup>2</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>3</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>4</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>5</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>6</sup> is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

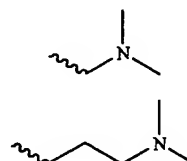
(ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.

iv) H, a halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

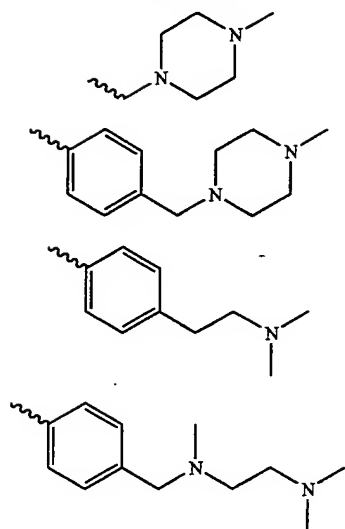
In another alternative, substituent R<sup>6</sup>, which in the formula II is connected to position 4 of the thiazole ring, may instead occupy position 5 of the thiazole ring.

Among the preferred compounds corresponding formula II, the invention is directed to compounds in which X is a substituted alkyl, aryl or heteroaryl group bearing a pendant basic nitrogen functionality represented for example by the structures a to f shown below, wherein the wavy line corresponds to the point of attachment to core structure of formula II:



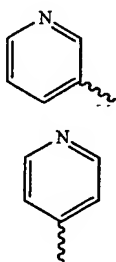
11

-continued



Among group a to f, X (see formula II) is preferentially group d.

Furthermore, among the preferred compounds of formula I or II, the invention concerns the compounds in which  $R^2$  and  $R^3$  are hydrogen. Preferentially,  $R^4$  is a methyl group and  $R^5$  is H. In addition,  $R^6$  is preferentially a 3-pyridyl group (cf. structure g below), or a 4-pyridyl group (cf. structure h below). The wavy line in structure g and h correspond to the point of attachment to the core structure of formula I or II.



Thus, the invention contemplates:

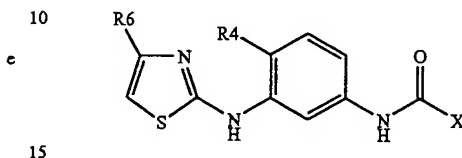
- 1—A compound of formula II as depicted above, wherein X is group d and  $R^6$  is a 3-pyridyl group.
- 2—A compound of formula II as depicted above, wherein X is group d and  $R^4$  is a methyl group.
- 3—A compound of formula I or II as depicted above, wherein  $R^1$  is group d and  $R^2$  is H.
- 4—A compound of formula I or II as depicted above, wherein  $R^1$  is group d and  $R^3$  is H.
- 5—A compound of formula I or II as depicted above, wherein  $R^1$  is group d and  $R^2$  and/or  $R^3$  and/or  $R^5$  is H.
- 6—A compound of formula I or II as depicted above, wherein  $R^6$  is a 3-pyridyl group and  $R^3$  is a methyl group.
- 7—A compound of formula I or II as depicted above, wherein  $R^6$  is a 3-pyridyl group and  $R^2$  is H.
- 8—A compound of formula I or II as depicted above, wherein  $R^2$  and/or  $R^3$  and/or  $R^5$  is H and  $R^4$  is a methyl group.

12

9—A compound of formula I or II as depicted above wherein  $R^2$  and/or  $R^3$  and/or  $R^5$  is H,  $R^4$  is a methyl group and  $R^6$  is a 3-pyridyl group.

Among the compounds of formula II, the invention is particularly embodied by the compounds wherein  $R^2$ ,  $R^3$ ,  $R^5$  are hydrogen, corresponding to the following formula II-1:

FORMULA II-1



wherein X is R or  $\text{NRR}'$  and wherein R and  $R'$  are independently chosen from H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl; an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a  $\text{—SO}_2\text{—R}$  group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a  $\text{—CO—R}$  or a  $\text{—CO—NRR}'$  group, wherein R and  $R'$  are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

$R^4$  is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

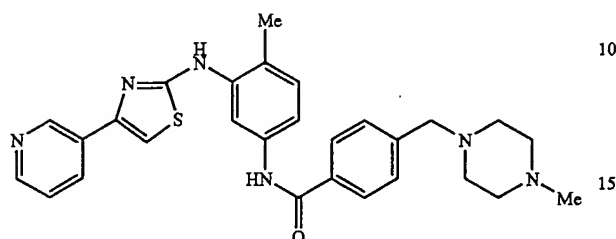
$R^6$  is one of the following:

- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.
- iv) H, a halogen selected from I, F, Cl or Br;  $\text{NH}_2$ ,  $\text{NO}_2$  or  $\text{SO}_2\text{—R}$ , wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

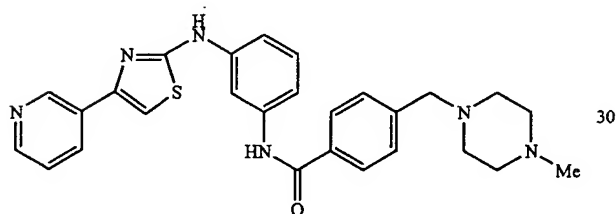
In another alternative, substituent  $R_6$ , which in the formula II is connected to position 4 of the thiazole ring, may instead occupy position 5 of the thiazole ring.

**13**  
EXAMPLES

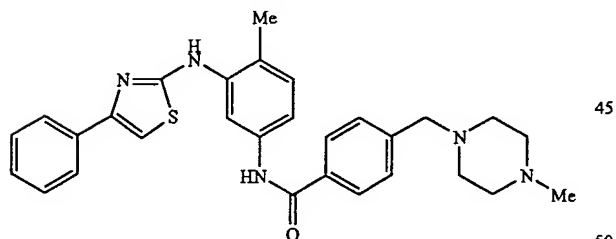
002: 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



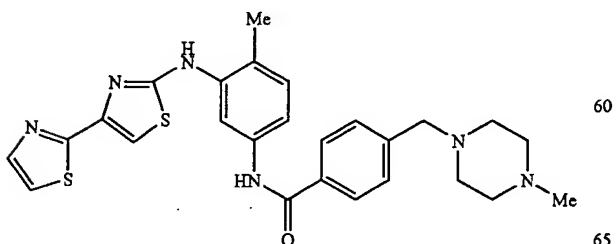
003: 4-(4-Methyl-piperazin-1-ylmethyl)-N-[3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



004: N-[4-Methyl-3-(4-phenyl-thiazol-2-ylamino)-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide

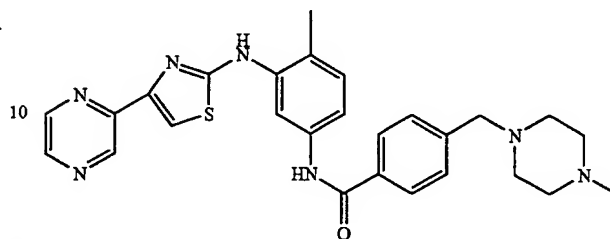


005: N-[3-([2,4']Bithiazolyl-2'-ylamino)-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide

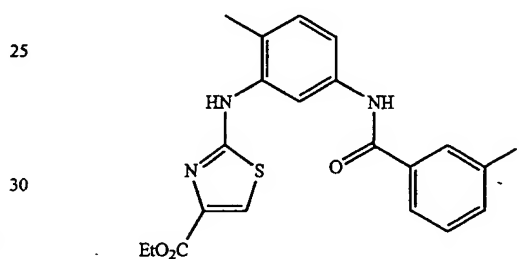


**14**

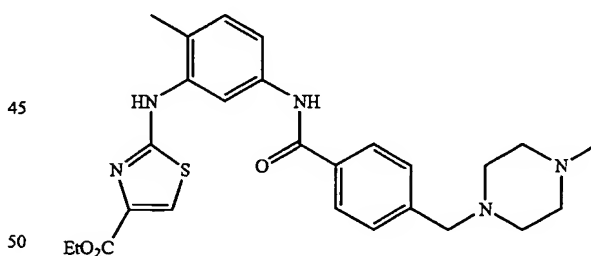
006: 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyrazin-2-yl-thiazol-2-ylamino)-phenyl]-benzamide



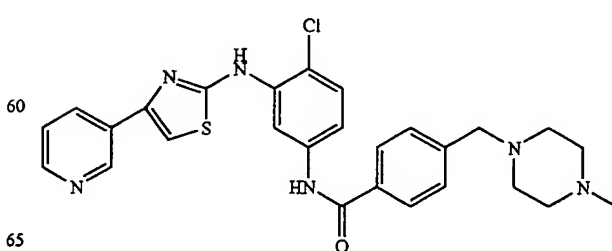
007: 2-[5-(3-Iodo-benzoylamino)-2-methyl-phenylamino]-thiazole-4-carboxylic acid ethyl ester



008: 2-{2-Methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-benzoylamino]-phenylamino}-thiazole-4-carboxylic acid ethyl ester

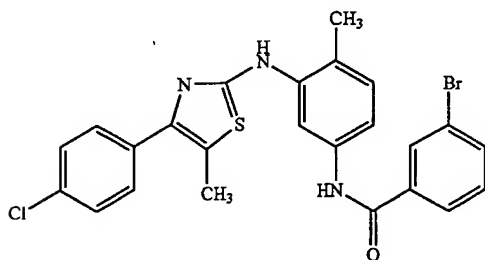


027: N-(4-chloro-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl)-4-(4-methyl-piperazin-1-ylmethyl)-benzamide

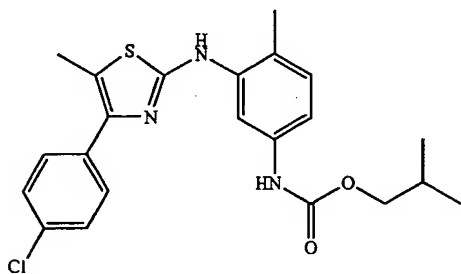


15

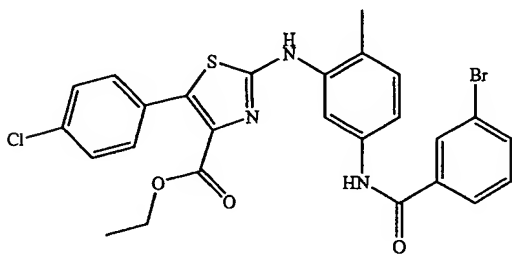
128: 3-Bromo-N-{3-[4-(4-chloro-phenyl)-5-methyl-thiazol-2-ylamino]-4-methyl-phenyl}-benzamide



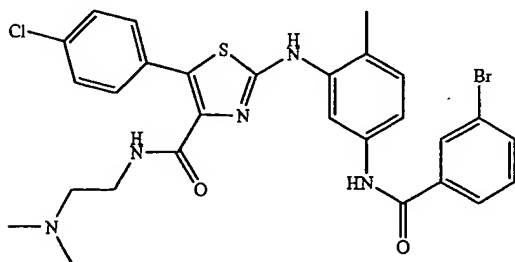
129: {3-[4-(4-Chloro-phenyl)-5-methyl-thiazol-2-ylamino]-4-methyl-phenyl}-carbamic acid isobutyl ester



130: 2-[5-(3-Bromo-benzoylamino)-2-methyl-phenylamino]-5-(4-chloro-phenyl)-thiazole-4-carboxylic acid ethyl ester

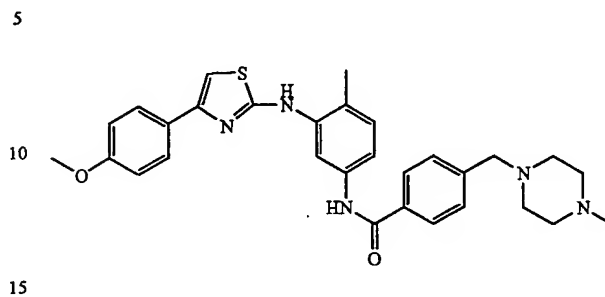


131: 2-[5-(3-Bromo-benzoylamino)-2-methyl-phenylamino]-5-(4-chloro-phenyl)-thiazole-4-carboxylic acid (2-dimethylamino-ethyl)-amide

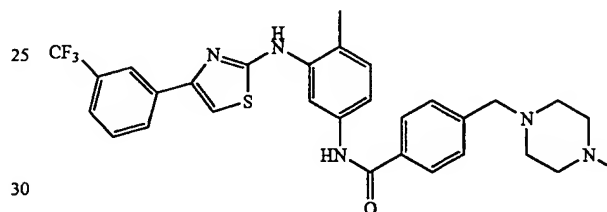


16

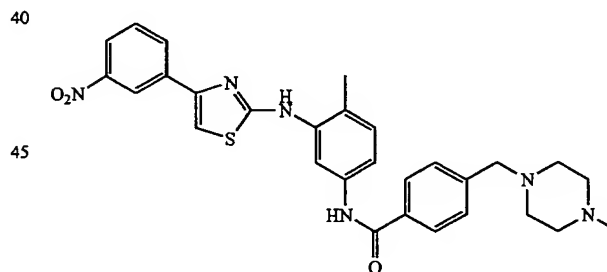
110: N-{3-[4-(4-Methoxy-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



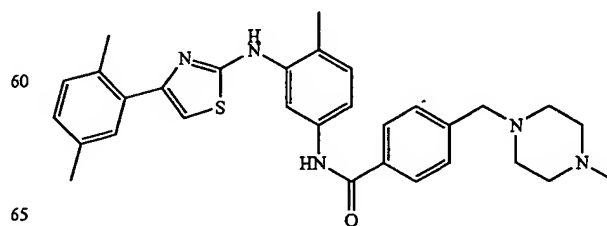
116: 4-(4-Methyl-piperazin-1-ylmethyl)-N-{4-methyl-3-[4-(3-trifluoromethyl-phenyl)-thiazol-2-ylamino]-phenyl}-benzamide



117: N-{4-Methyl-3-[4-(3-nitro-phenyl)-thiazol-2-ylamino]-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



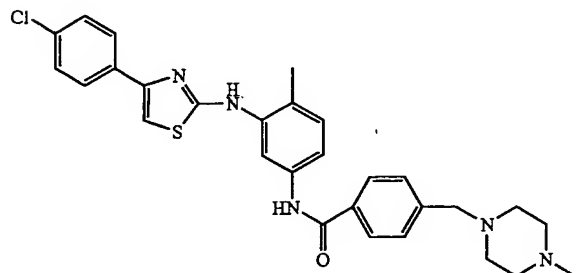
124: N-{3-[4-(2,5-Dimethyl-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide





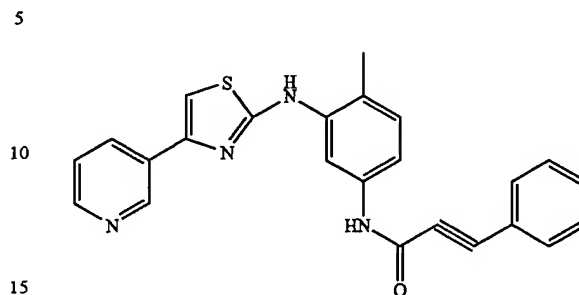
17

108: N-{3-[4-(4-Chloro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide

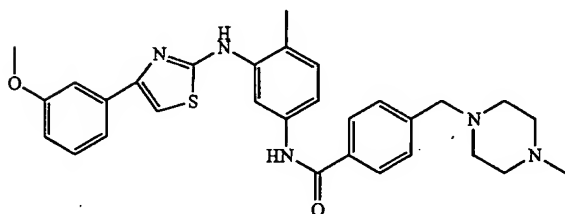


18

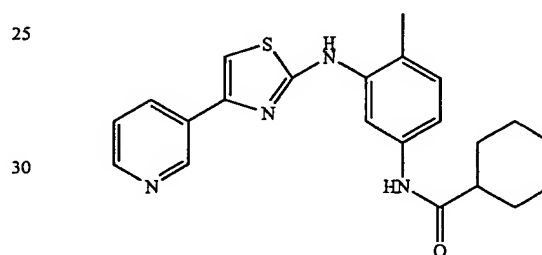
091: 3-Phenyl-propynoic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide



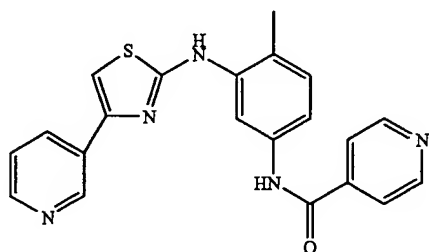
113: N-{3-[4-(3-Methoxy-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



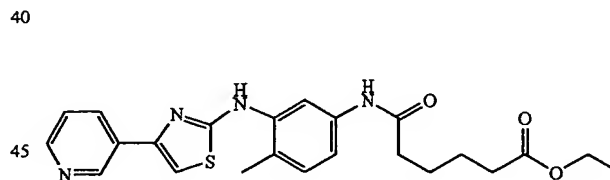
092: Cyclohexanecarboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide



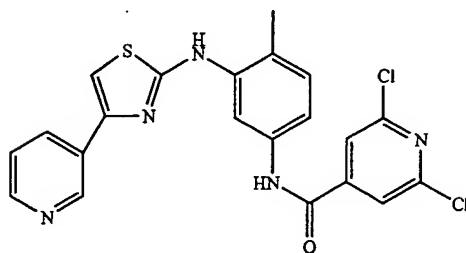
063: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-isonicotinamide



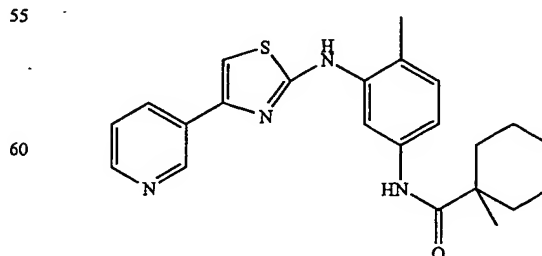
093: 5-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-pentanoic acid ethyl ester



064: 2,6-Dichloro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-isonicotinamide

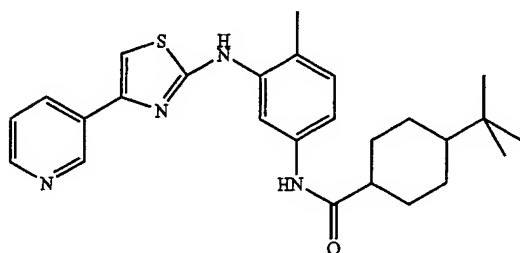


094: 1-Methyl-cyclohexanecarboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide



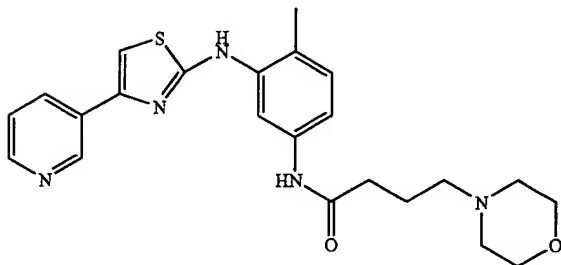
19

095: 4-tert-Butyl-cyclohexanecarboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide



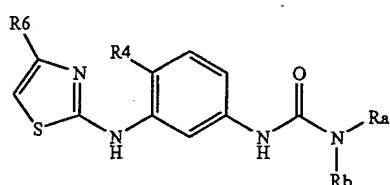
mixture of isomers  
cis/trans

096: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-morpholin-4-yl-butyramide



beige powder mp: 116-120° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>)  
δ=1.80-2.00 (m, 2H); 2.29 (s, 3H); 2.30-2.45 (m, 6H); 3.55-3.65 (m, 6H); 7.15-7.25 (m, 2H); 7.46-7.50 (m, 2H); 7.52 (s, 1H); 8.35 (d, J=6.2 Hz, 1H); 8.55 (dd, J=1.5 Hz, J=4.7 Hz, 2H); 9.22 (s, 1H); 9.45 (s, 1H); 9.93 (s, 1H)

Among the compounds of formula II, the invention is particularly embodied by the compounds wherein X is a urea group, a —CO—NRR' group, corresponding to the [3-(thiazol-2-ylamino)-phenyl]-urea family and the following formula II-2:



FORMULA II-2

wherein Ra, Rb are independently chosen from H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

20

a —SO<sub>2</sub>-R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a —CO—R or a —CO—NRR' group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, or bearing a pendant basic nitrogen functionality.

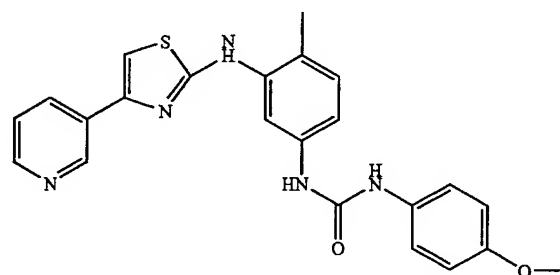
R<sup>4</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>6</sup> is one of the following:

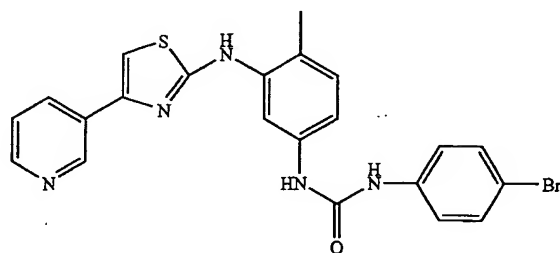
- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.
- iv) H, a halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

## EXAMPLES

009: 1-(4-Methoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

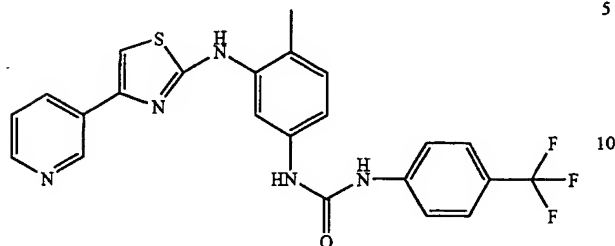


010: 1-(4-Bromo-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



21

011: 1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(4-trifluoromethyl-phenyl)-urea



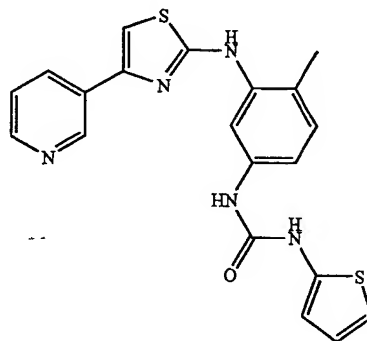
5

10

15

22

015: 1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-thiophen-2-yl-urea

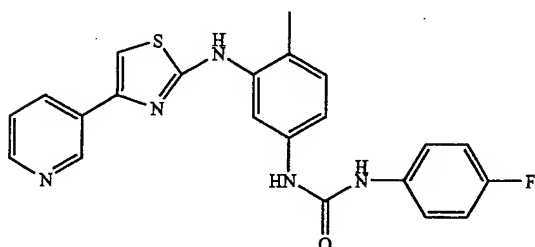


20

25

30

012: 1-(4-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

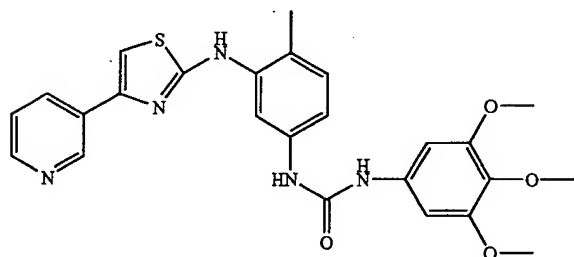


35

40

45

013: 1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(3,4,5-trimethoxy-phenyl)-urea



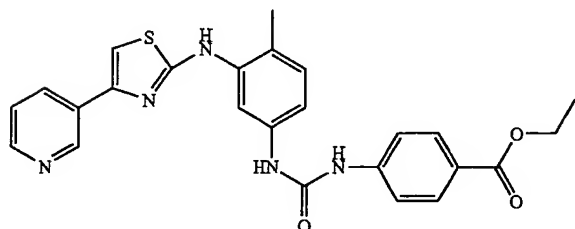
50

55

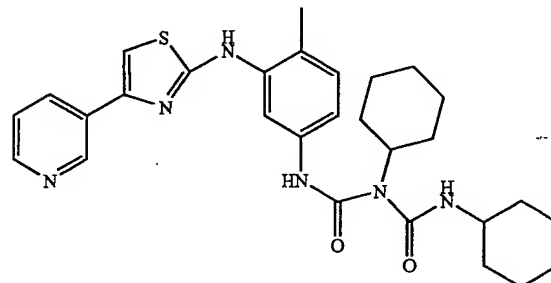
60

65

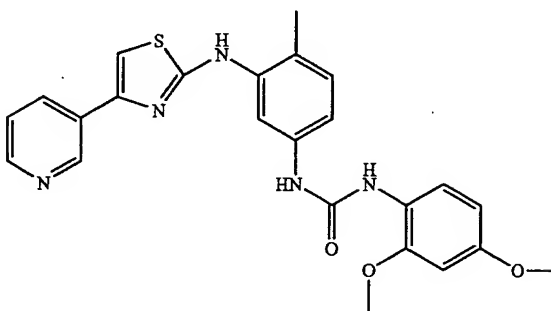
014: 4-{3-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-ureido}-benzoic acid ethyl ester



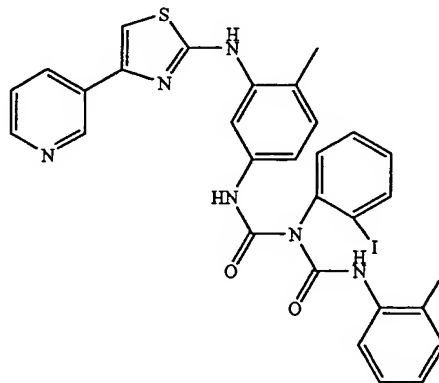
016: 1-Cyclohexyl-1-(N-Cyclohexyl-formamide)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



017: 1-(2,4-Dimethoxy-phenyl)-3-[4-methyl-2-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

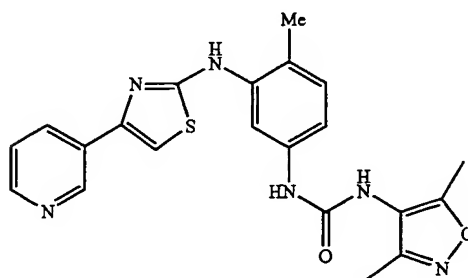


018: 1-(2-Iodo-phenyl)-1-(N-(2-Iodo-phenyl)-formamide)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

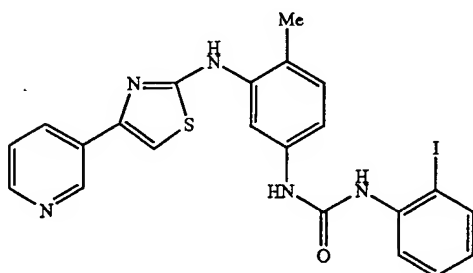


23

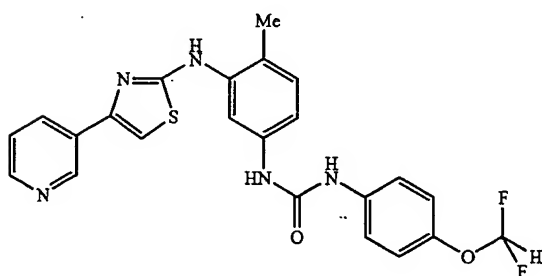
019: 1-(3,5-Dimethyl-isoxazol-4-yl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



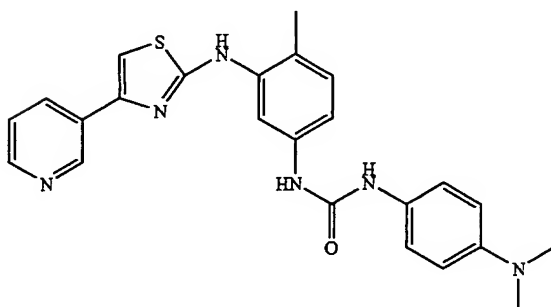
020: 1-(2-Iodo-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



021: 1-(4-Difluoromethoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

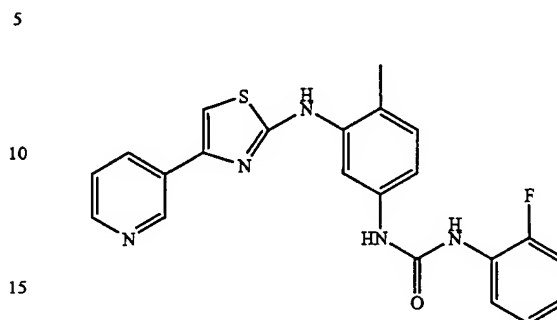


022: 1-(4-Dimethylamino-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



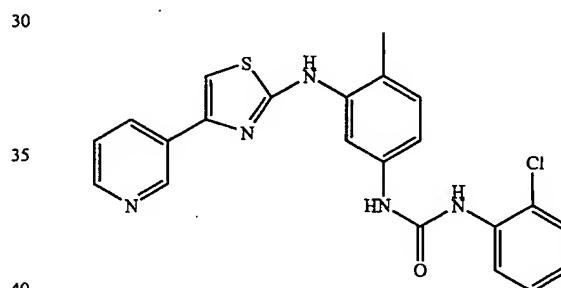
24

023: 1-(2-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

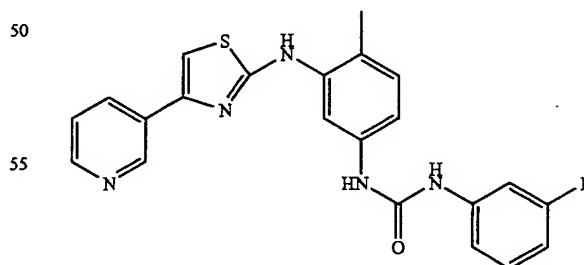


light brown powder mp: 203-206° C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ=2.24 (s, 3H); 6.98-7.00 (m, 2H); 7.10-7.23 (m, 3H); 7.40 (m, 1H); 7.48 (s, 1H); 8.25 (m, 1H); 8.37 (d, J=7.8 Hz, 1H); 8.51 (m, 3H); 9.03 (s, 1H); 9.19 (s, 1H); 9.39 (s, 1H)

024: 1-(2-Chloro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



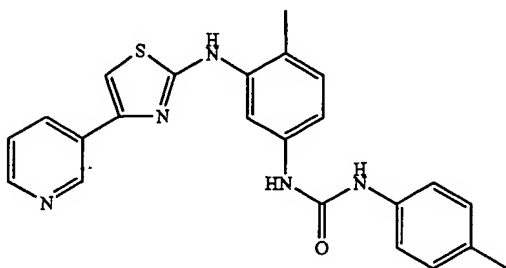
025: 1-(3-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



white powder mp: 210-215° C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.24 (s, 3H); 6.79 (t, J=6.3 Hz, 1H); 6.99 (m, 1H); 7.09-7.14 (m, 2H); 7.30 (m, 1H); 7.41 (t, J=4.7 Hz, 1H); 7.48 (s, 1H); 7.56 (d, J=1.2 Hz, 1H); 8.39 (d, J=8.0 Hz, 1H); 8.49-8.52 (m, 2H); 8.71 (s, 1H); 8.87 (s, 1H); 9.18 (s, 1H); 9.38 (s, 1H)

25

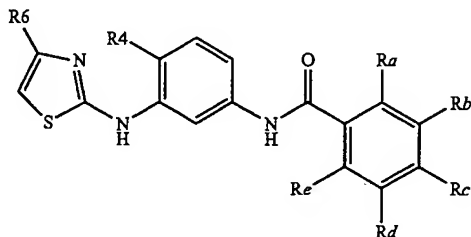
026: 1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-p-tolyl-urea



white powder mp: 238-240° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.29 (s, 3H); 2.31 (s, 3H); 7.05 (d, J=6.2 Hz, 1H); 7.10-1.16 (m, 3H); 7.42-7.49 (m, 3H); 7.53 (s, 1H); 8.35-8.62 (m, 5H); 9.22 (d, J=1.6 Hz, 1H); 9.43 (s, 1H)

Among the compounds of formula II, the invention is particularly embodied by the compounds wherein X is a substituted Aryl group, corresponding to the N-[3-(Thiazol-2-ylamino)-phenyl]-amide family and the following formula II-3:

FORMULA II-3



wherein Ra, Rb, Rc, Rd, Re are independently chosen from H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a —SO<sub>2</sub>-R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a —CO—R or a —CO—NRR' group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

Ra, Rb, Rc, Rd, Re may also be a halogen such as I, Cl, Br and F

a NRR' group where R and R' are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a

26

cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

an OR group where R is H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; a —SO<sub>2</sub>-R' group wherein R' is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a NRaCORb group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a NRaCONRbRc group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; a COOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

a CONRaRb, where Ra and Rb are a hydrogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at

27

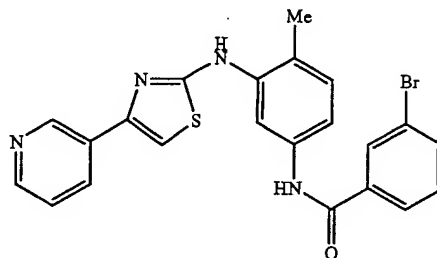
- least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;
- an NHCOOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;
- an OSO<sub>2</sub>R, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;
- an NRaOSO<sub>2</sub>Rb, where Ra and Rb are a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; Ra can also be a hydrogen; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;
- a CN group
- a trifluoromethyl group
- R<sup>4</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;
- R<sup>6</sup> is one of the following:
- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
  - (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
  - (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

28

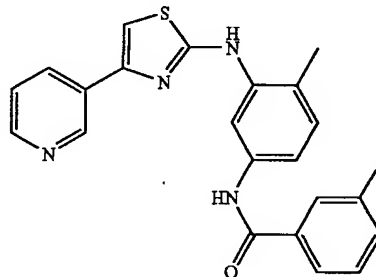
- iv) H, a halogen selected from I, F, Cl or Br, NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

## EXAMPLES

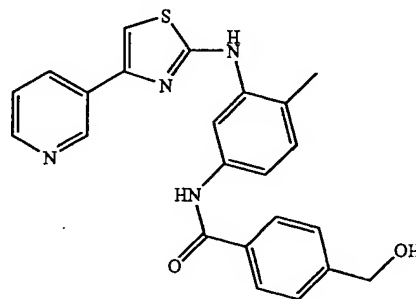
- 028: 3-Bromo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



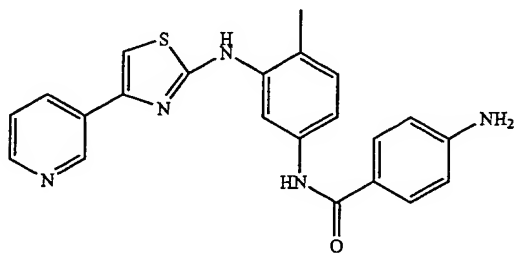
- 029: 3-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



- 030: 4-Hydroxymethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

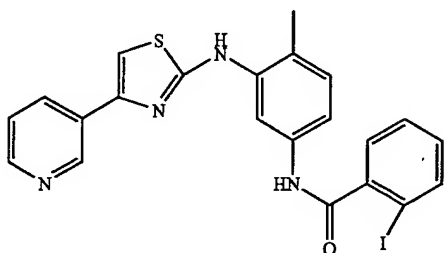


- 031: 4-Amino-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



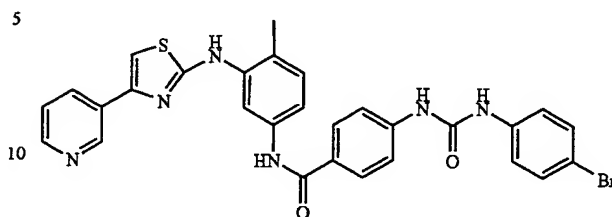
29

032: 2-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

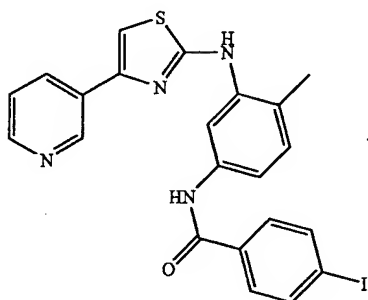


30

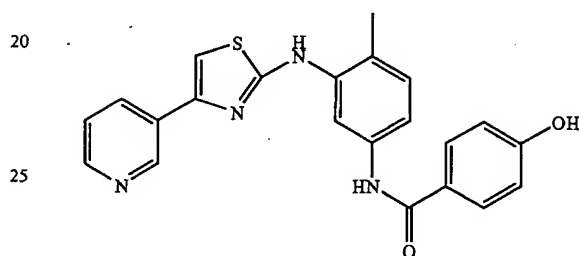
036: 4-[3-(4-Bromo-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



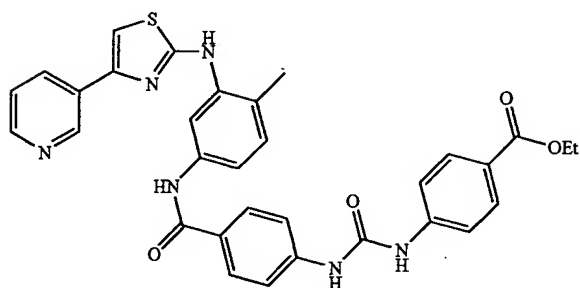
033: 4-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



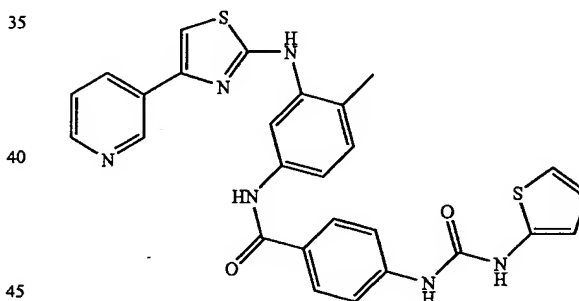
037: 4-Hydroxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



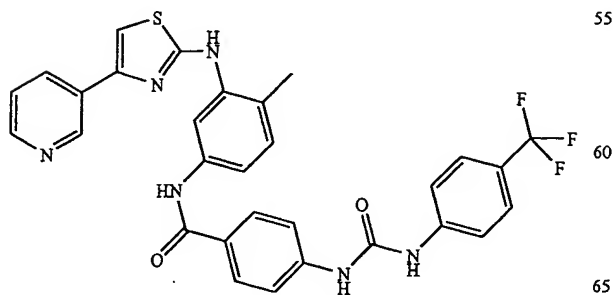
034: 4-(3-{4-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl}-ureido)-benzoic acid ethyl ester



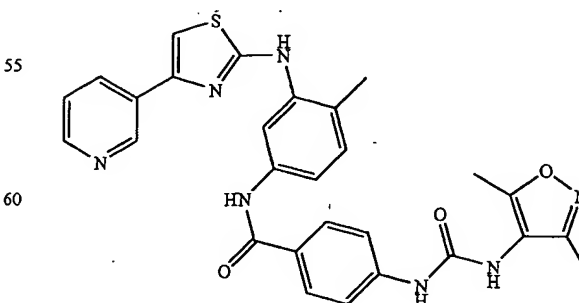
038: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-(3-thiophen-2-yl-ureido)-benzamide



035: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide

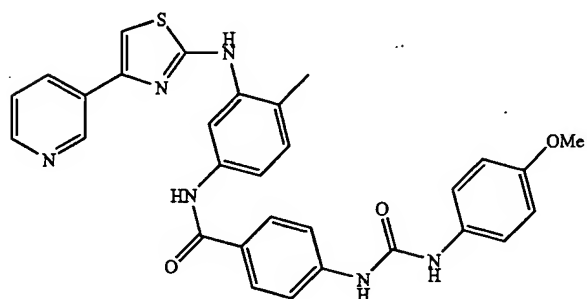


039: 4-[3-(3,5-Dimethyl-isoxazol-4-yl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

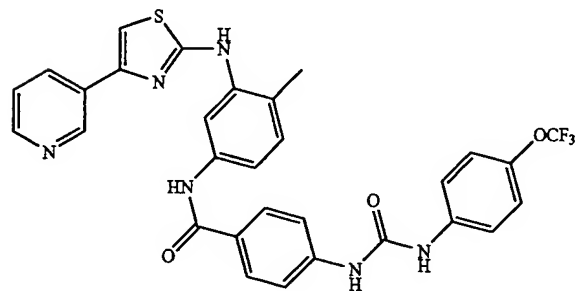


31

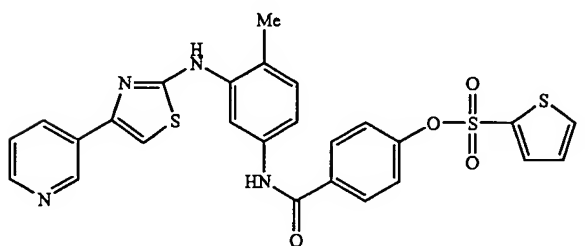
040: 4-[3-(4-Methoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



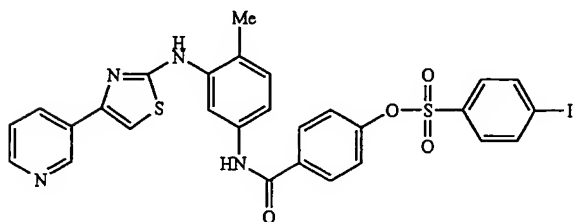
041: 4-[3-(4-Difluoromethoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



042: Thiophene-2-sulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester

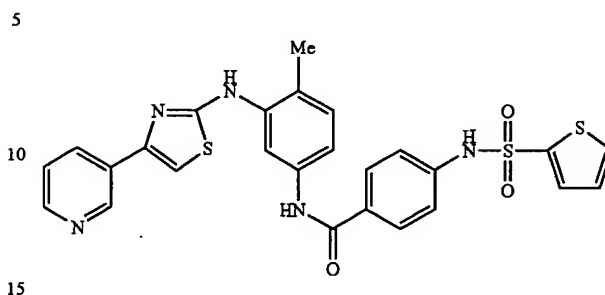


043: 4-Iodo-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester



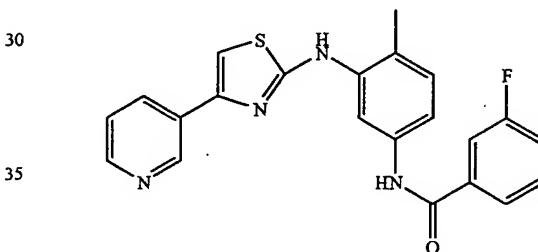
32

044: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]4-(thiophene-2-sulfonylamino)-benzamide



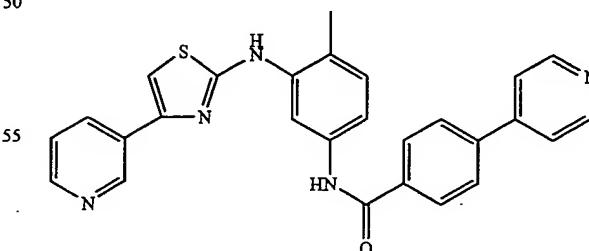
brown powder mp: 230-233° C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  
 δ=2.29 (s, 3H); 7.15-7.18 (m, 2H); 7.22-7.32 (m, 3H); 7.48  
 (m, 2H); 7.67 (dd, J=1.3 Hz, J=3.7 Hz, 1H); 7.90-7.96 (m,  
 3H); 8.38-8.42 (m, 1H); 8.51 (m, 1H); 8.57 (d, J=1.9 Hz, 1H);  
 9.17 (d, J=1.7 Hz, 1H); 9.44 (s, 1H); 10.12 (s, 1H); 10.82 (s,  
 1H)

045: 3-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



off-white foam mp: 184-186° C. <sup>1</sup>H NMR (CD<sub>3</sub>OD-d<sub>4</sub>):  
 δ=2.23 (s, 3H); 7.12-7.14 (m, 2H); 7.20-7.23 (m, 2H); 7.30  
 (m, 1H); 7.43 (m, 1H); 7.50 (m, 1H); 7.66 (d, J=1.0 Hz, 1H);  
 8.23 (m, 1H); 8.33 (m, 1H); 8.38 (s, 1H); 8.98 (s, 1H)

046: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]4-pyridin-4-yl-benzamide

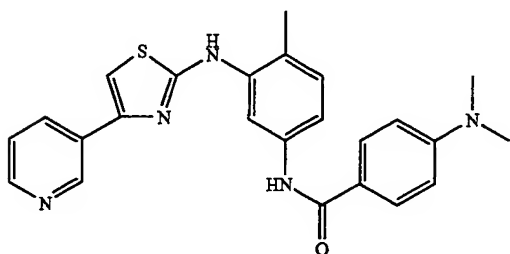


yellow powder mp: 254-256° C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ  
 2.34 (s, 3H); 7.28 (d, J=8.0 Hz, 1H); 7.45-7.49 (m, 2H); 7.54  
 (s, 1H); 7.78 (t, J=7.6 Hz, 1H); 7.89-7.91 (m, 2H); 8.10 (t,  
 J=7.8 Hz, 2H); 8.37-8.42 (m, 2H); 8.55 (d, J=4.7 Hz, 1H);  
 8.73-8.77 (m, 3H); 9.24 (s, 1H); 9.52 (s, 1H); 10.43 (s, 1H)



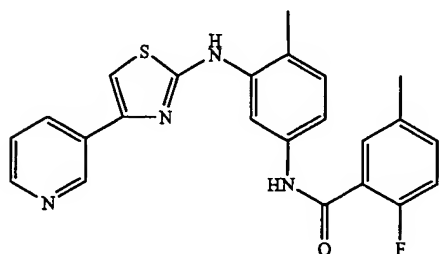
33

047: 4-Dimethylamino-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



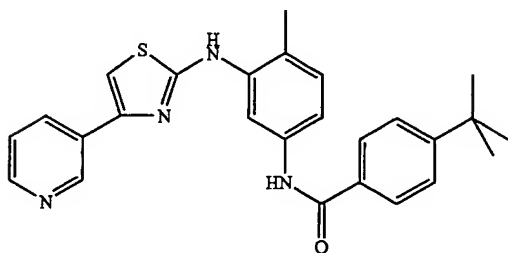
beige powder mp: 147-150° C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.25 (s, 3H); 2.99 (s, 6H); 6.76 (d, J=8.9 Hz, 2H); 7.16 (d, J=8.3 Hz, 1H); 7.35 (d, J=2.0 Hz, 1H); 7.44-7.47 (m, 2H); 7.86-7.89 (m, 2H); 8.34-8.36 (m, 1H); 8.48-8.50 (m, 1H); 8.56-8.57 (m, 1H); 9.16 (s, 1H); 9.44 (s, 1H); 9.85 (s, 1H)

048: 2-Fluoro-5-methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



brown orange powder mp: 103-106° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.26 (s, 3H); 2.35 (s, 3H); 7.17-7.47 (m, 7H); 8.29 (dd, J=1.6 Hz, J=7.9 Hz, 1H); 8.47 (d, J=3.5 Hz, 1H); 8.57 (s, 1H); 9.15 (d, J=2.0 Hz, 1H); 9.44 (s, 1H); 10.33 (s, 1H)

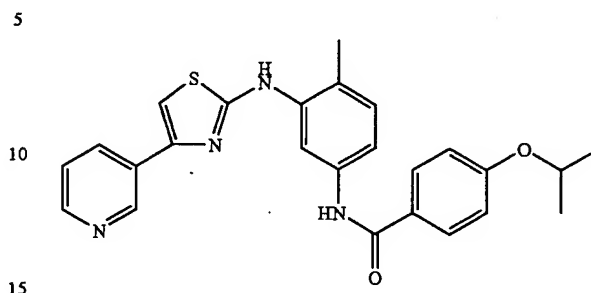
049: 4-tert-Butyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



brown powder mp: 145-150° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=1.32 (s, 9H); 2.04 (s, 3H); 7.18 (d, J=8.4 Hz, 1H); 7.35-7.44 (m, 2H); 7.46 (s, 1H); 7.55 (d, J=8.5 Hz, 1H); 7.90 (d, J=8.5 Hz, 1H); 8.32 (d, J=7.9 Hz, 1H); 8.47 (dd, J=1.5 Hz, J=4.7 Hz, 1H); 8.60 (d, J=2.0 Hz, 1H); 9.15 (d, J=1.7 Hz, 1H); 9.43 (s, 1H); 10.15 (s, 1H)

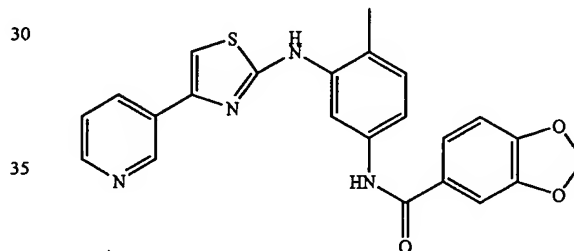
34

050: 4-Isopropoxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



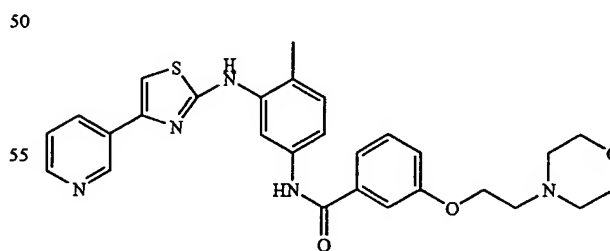
brown powder mp: 154-155° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=1.34 (d, J=5.9 Hz, 6H); 4.72 (hept, J=5.9 Hz, 1H); 7.01 (d, J=7.0 Hz, 2H); 7.18 (d, J=8.5 Hz, 1H); 7.35-7.44 (m, 2H); 7.46 (s, 1H); 7.94 (dd, J=2.0 Hz, J=6.7 Hz, 2H); 8.32 (d, J=8.3 Hz, 1H); 8.48 (dd, J=3.3 Hz, J=4.8 Hz, 1H); 8.58 (d, J=2.0 Hz, 1H); 9.15 (d, J=1.8 Hz, 1H); 9.43 (s, 1H); 10.4 (s, 1H)

051: Benzo[1,3]dioxole-5-carboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide



brown orange powder mp: 130-132° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.23 (s, 3H); 6.10 (s, 2H); 7.03 (d, J=8.1 Hz, 1H); 7.15 (d, J=8.3 Hz, 1H); 7.25-7.55 (m, 6H); 8.26 (s, 1H); 8.45 (dd, J=1.5 Hz, J=4.7, 1H); 8.55 (d, J=2.0 Hz, 1H); 9.12 (d, J=1.7 Hz, 1H); 9.40 (s, 1H); 10.01 (s, 1H)

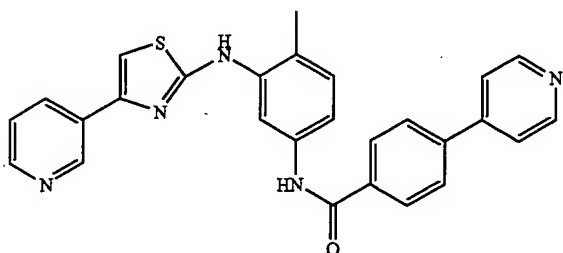
052: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(2-morpholin-4-yl-ethoxy)-benzamide



beige yellow powder mp: 75-80° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.10-2.25 (m, 4H); 2.50-2.60 (m, 2H); 3.19 (s, 3H); 3.41-3.48 (m, 4H); 4.00-4.06 (m, 2H); 7.00-7.11 (m, 2H); 7.22-7.35 (m, 6H); 8.18 (d, J=8.0 Hz, 1H); 8.33 (d, J=0.9 Hz, 1H); 8.49 (d, J=1.7 Hz, 1H); 9.03 (s, 1H); 9.31 (s, 1H); 10.05 (s, 1H)

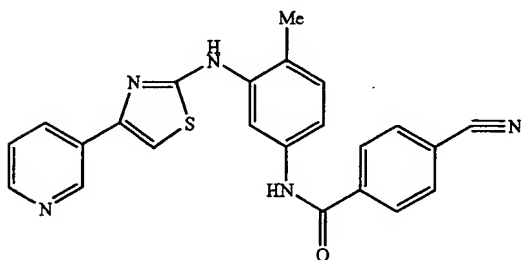
35

053: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-pyridin-4-yl-benzamide

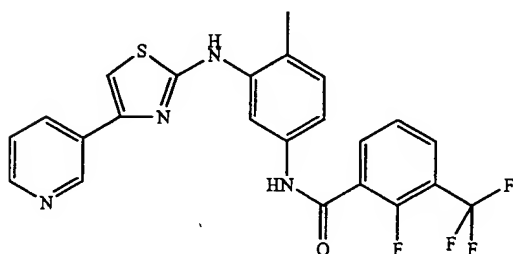


brown powder mp: dec. 250° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.28 (s, 3H); 7.21 (d, J=7.9 Hz, 1H); 7.30-7.50 (m, 3H) 7.81 (d, J=4.7 Hz, 1H); 7.98 (d, J=7.5 Hz, 2H); 8.13 (d, J=7.9 Hz, 2H); 8.32 (d, J=7.7 Hz, 1H); 8.48 (d, J=4.9 Hz, 1H); 8.62-8.69 (m, 3H); 9.16 (s, 1H); 9.45 (s, 1H) 10.34 (s, 1H)

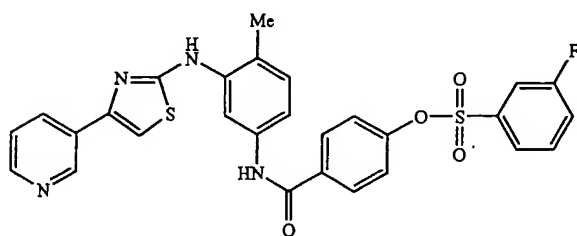
054: 3-Cyano-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



055: 2-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide

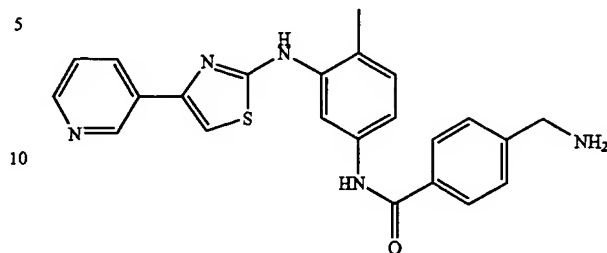


056: 3-Fluoro-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester

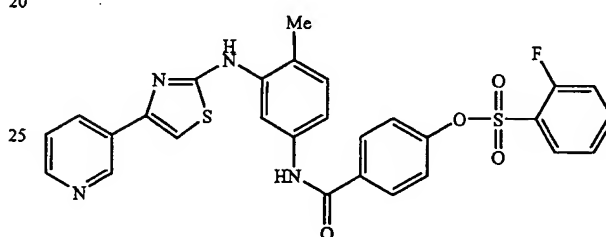


36

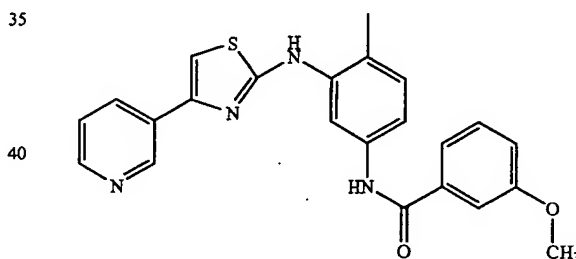
057: 4-Aminomethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



058: 2-Fluoro-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester

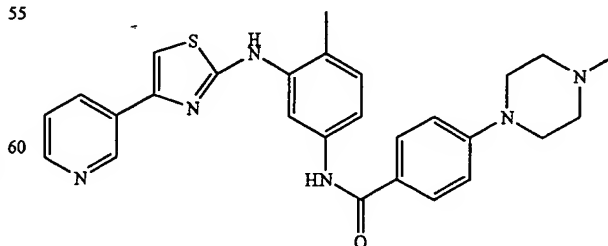


059: 3-Methoxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



white powder mp: 76-79° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.32 (s, 3H); 3.89 (s, 3H); 7.22-7.25 (m, 2H); 7.44-7.58 (m, 4H); 8.28-8.35 (m, 1H); 8.52 (dd, J=1.6 Hz, J=4.7 Hz, 1H); 8.66 (d, J=2.0 Hz, 1H); 9.20 (d, J=1.4 Hz, 1H); 9.50 (s, 1H); 10.25 (s, 1H)

060: 4-(4-Methyl-piperazin-1-yl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-benzamide

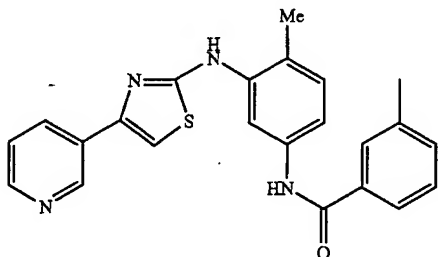


beige brown powder mp: 128-130° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.15 (s, 3H); 2.18 (s, 3H); 2.35-2.41 (m, 4H); 3.18-

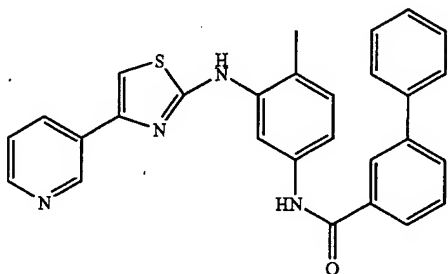
37

3.3.24 (m, 4H); 6.94 (d, J=8.9 Hz, 2H); 7.09 (d, J=8.4 Hz, 1H); 7.28-7.38 (m, 3H); 7.81 (d, J=8.9 Hz, 2H); 8.20-8.25 (m, 1H); 8.40 (dd, J=1.6 Hz, J=4.7, 1H); 8.48 (d, J=1.9 Hz, 1H); 9.07 (d, J=1.5 Hz, 1H); 9.35 (s, 1H); 9.84 (s, 1H)

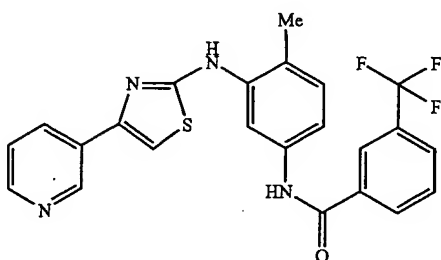
061: 3-Methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



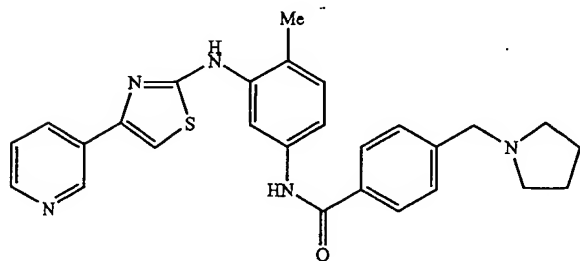
062: Biphenyl-3-carboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide



065: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide

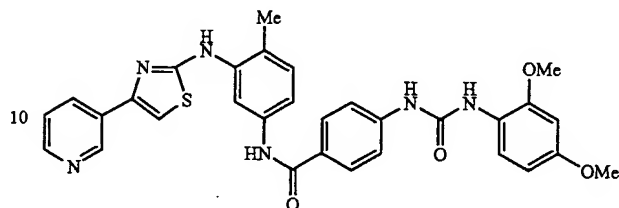


099: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-pyrrolidin-1-ylmethyl-benzamide

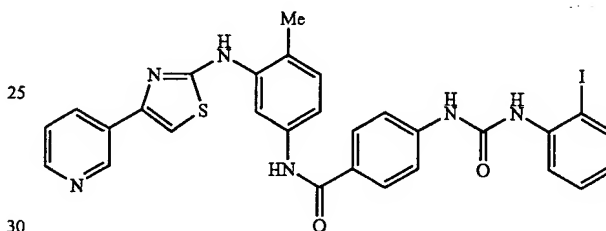


38

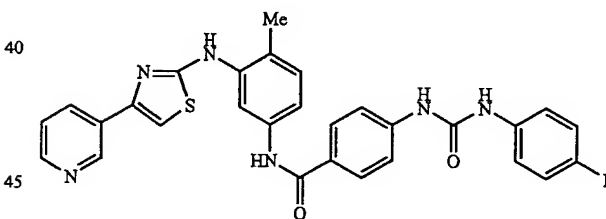
100: 4-[3-(2,4-Dimethoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



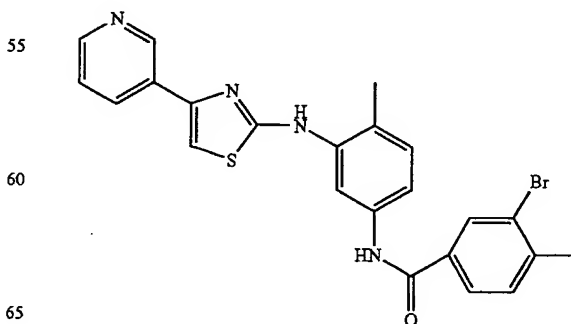
101: 4-[3-(2-Iodo-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



102: 4-[3-(4-Fluoro-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

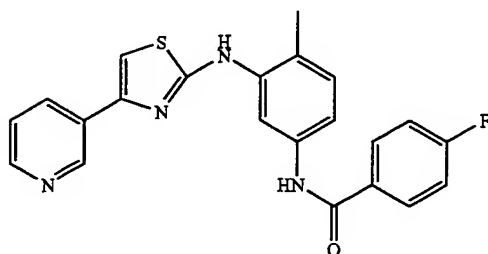


105: 3-Bromo-4-methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

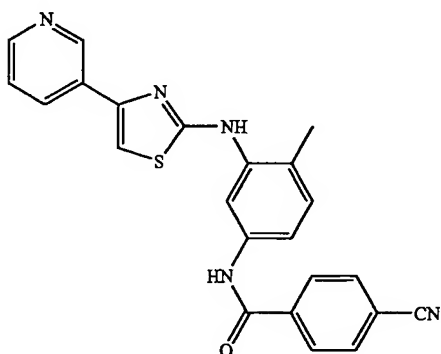


39

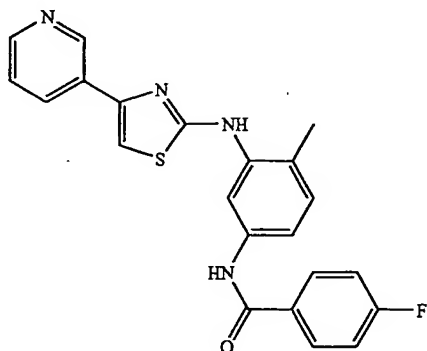
106: 4-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



103: 4-Cyano-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



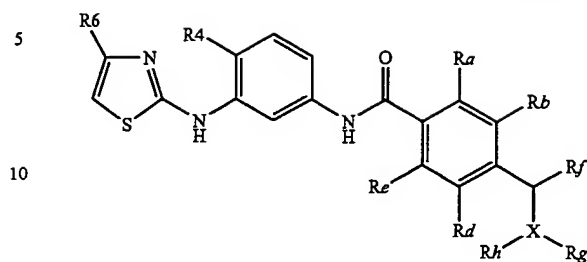
104: 4-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



Among compounds of formula II, the invention is particularly embodied by the compounds wherein X is a substituted-aryl group, corresponding to the 4-(4-substituted-1-ylmethyl)-N-[3-(thiazol-2-ylamino)-phenyl]-benzamide family and the following formula II-4:

40

FORMULA II-4



wherein X is a heteroatom, such as O or N

wherein Ra, Rb, Rd, Re, Rf, Rh are independently chosen from H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

or a NRR' group where R and R' are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or an OR group where R is H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; a —SO<sub>2</sub>-R' group wherein R' is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

or a NRaCORb group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with

41

an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a  $\text{NRaCONRbRc}$  group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

or a COOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

or a CONRaRb, where Ra and Rb are a hydrogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

or an NHCOOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and I or bearing a pendant basic nitrogen functionality;

an  $\text{OSO}_2\text{R}$ , where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

42

or an  $\text{NRaOSO}_2\text{Rb}$ , where Ra and Rb are a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; Ra can also be a hydrogen; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

or a  $\text{—SO}_2\text{—R}$  group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a  $\text{—CO—R}$  or a  $\text{—CO—NRR'}$  group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

Ra, Rb, Rd, Re can also be halogen such as Cl, F, Br, I or trifluoromethyl;

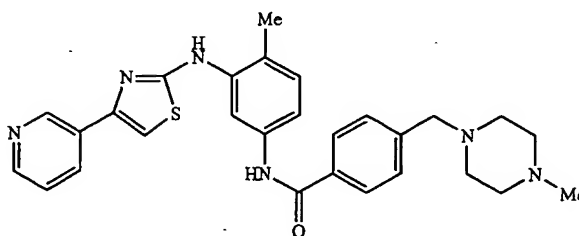
$\text{R}^4$  is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

$\text{R}^6$  is one of the following:

- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- iv) H, a halogen selected from I, F, Cl or Br;  $\text{NH}_2$ ,  $\text{NO}_2$  or  $\text{SO}_2\text{—R}$ , wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

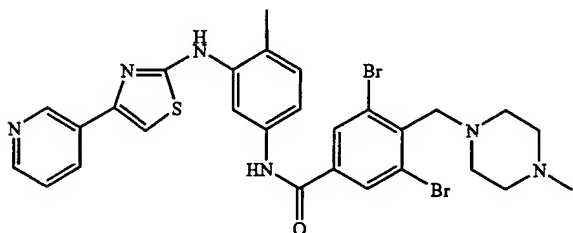
## EXAMPLES

066: 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

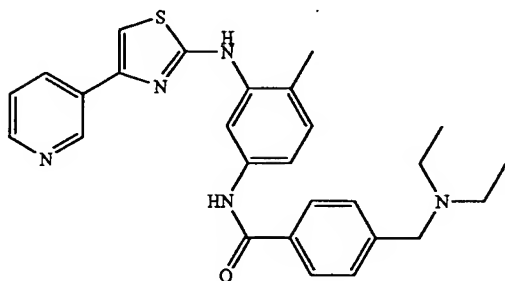


43

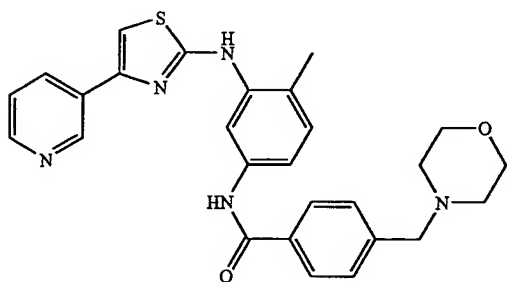
067: 3,5-Dibromo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



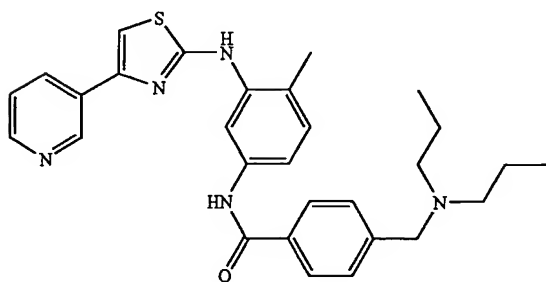
068: 4-Diethylaminomethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



069: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-morpholin-4-ylmethyl-benzamide

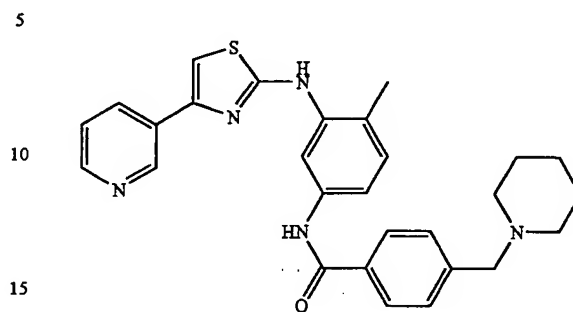


070: 4-Dipropylaminomethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

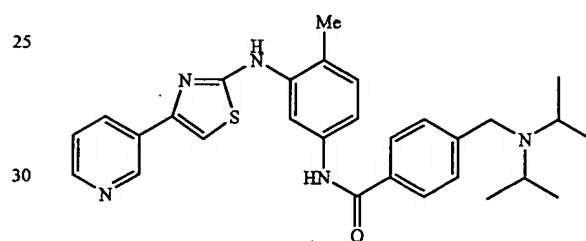


44

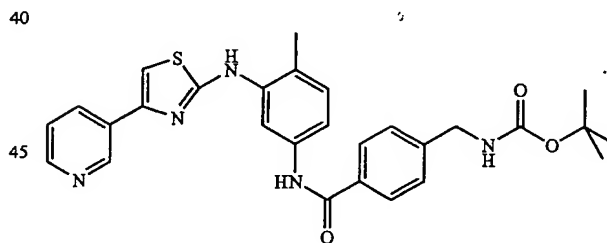
071: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-piperidin-1-ylmethyl-benzamide



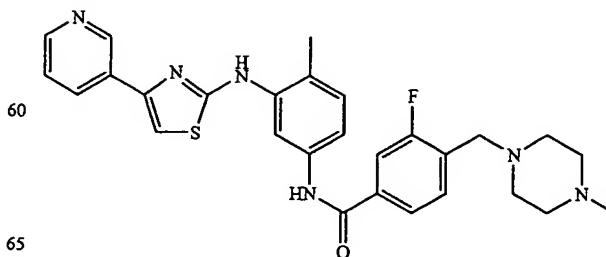
072: 4-[(Diisopropylamino)-methyl]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



073: {4-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-benzyl}-carbamic acid tert-butyl ester

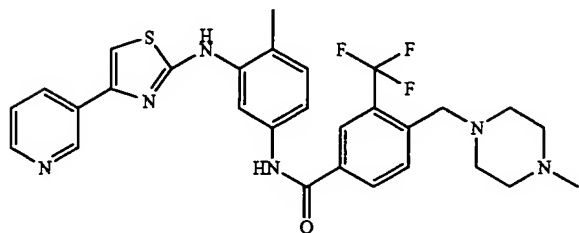


074: 3-Fluoro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



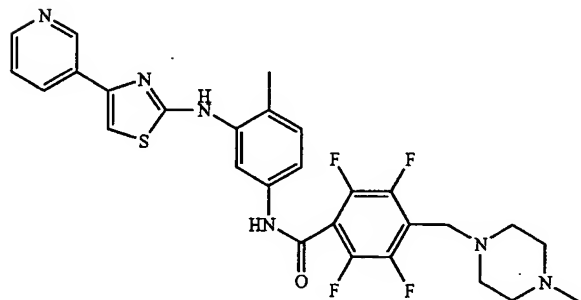
45

075: 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide

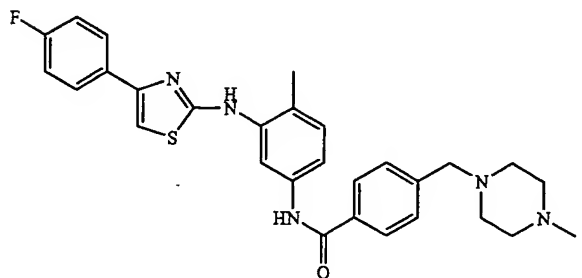


yellow crystals mp: 118-120° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.22 (s, 3H); 2.33 (s, 3H); 2.34-2.50 (m, 8H); 3.74 (s, 2H); 7.26 (d, J=8.3 Hz, 1H); 7.41-7.49 (m, 2H); 7.53 (s, 1H); 7.99 (d, J=8.0 Hz, 1H); 8.28-8.31 (m, 2H); 8.38 (d, J=7.9 Hz, 1H); 8.53 (dd, J=1.3 Hz, J=4.7 Hz, 1H); 8.68 (d, J=1.9 Hz, 1H); 9.21 (d, J=2.0 Hz, 1H); 9.53 (s, 1H); 10.49 (s, 1H)

076: 2,3,5,6-Tetrafluoro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

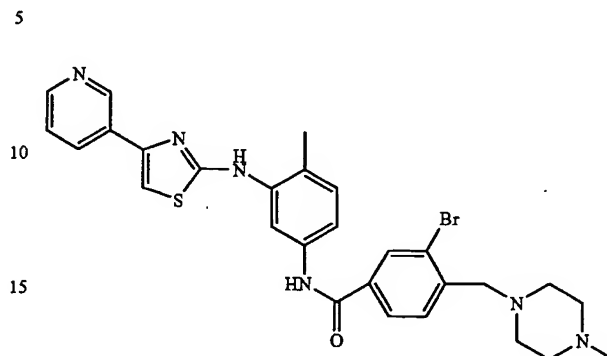


077: N-{3-[4-(4-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide

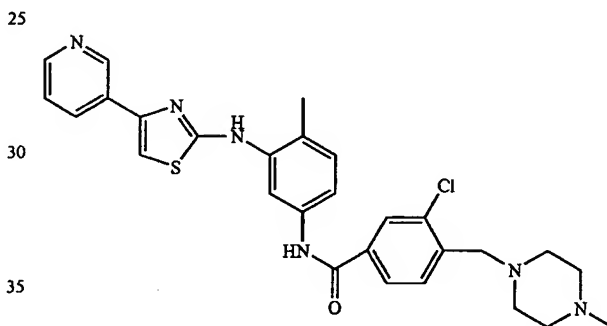


46

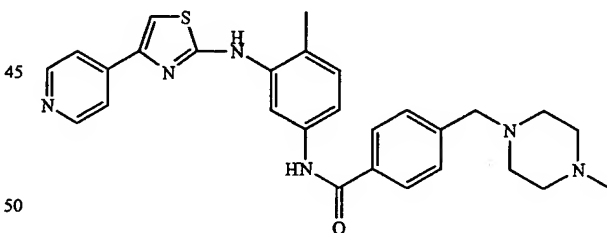
078: 3-Bromo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



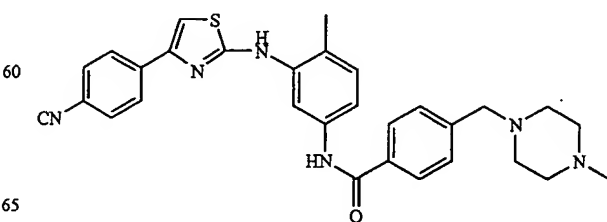
079: 3-Chloro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



080: 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-4-yl-thiazol-2-ylamino)-phenyl]-benzamide

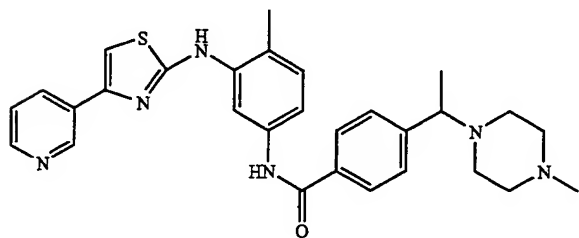


081: N-{3-[4-(4-Cyano-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



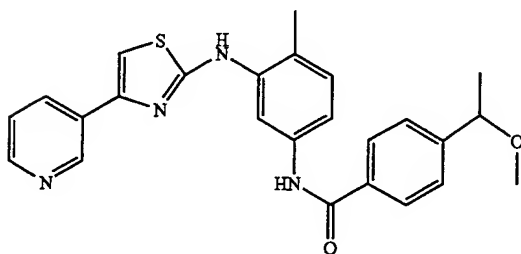
47

082: 4-[1-(4-Methyl-piperazin-1-yl)-ethyl]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

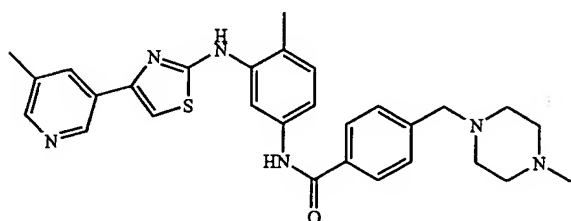


beige powder mp: 153-155° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>)  
 δ=1.29 (d, J=6.6 Hz, 3H); 2.15 (s, 3H); 2.26 (s, 3H); 3.15-3.25 (m, 9H); 7.18 (d, J=8.4 Hz, 1H); 7.35-7.47 (m, 5H); 7.91 (d, J=8.2 Hz, 2H); 8.31 (d, J=8.0 Hz, 1H); 8.47 (dd, J=1.6 Hz, J=4.7 Hz, 1H); 8.60 (d, J=2.0, 1H); 9.15 (d, J=0.6, 1H); 9.45 (s, 1H); 10.18 (s, 1H)

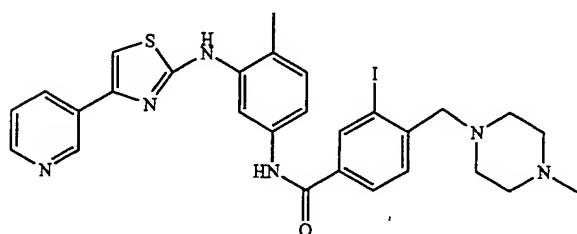
083: 4-(1-Methoxy-ethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



084: N-[4-Methyl-3-[4-(5-methyl-pyridin-3-yl)-thiazol-2-ylamino)-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide

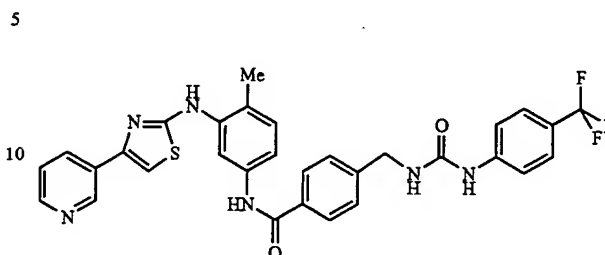


085: 3-Iodo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

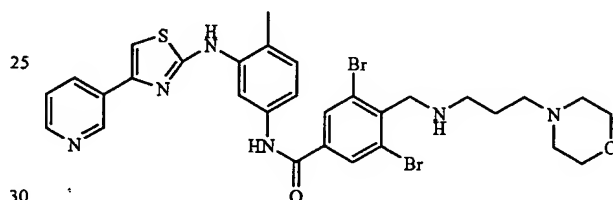


48

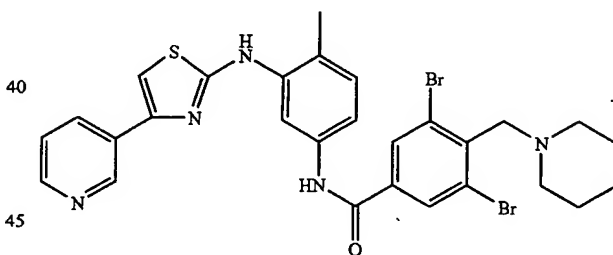
086: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[3-(4-trifluoromethyl-phenyl)-ureidomethyl]-benzamide



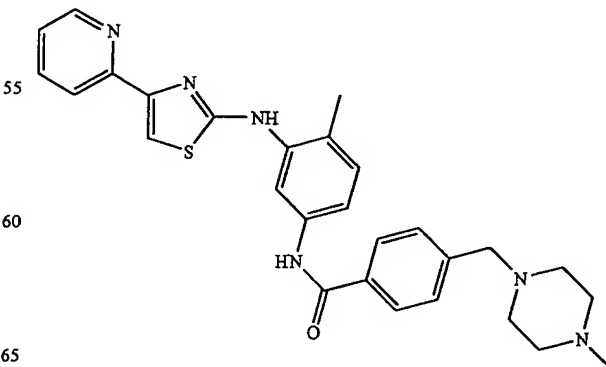
087: 3,5-Dibromo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[(3-morpholin-4-yl-propylamino)-methyl]-benzamide



107: 3,5-Dibromo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-piperidin-1-ylmethyl-benzamide



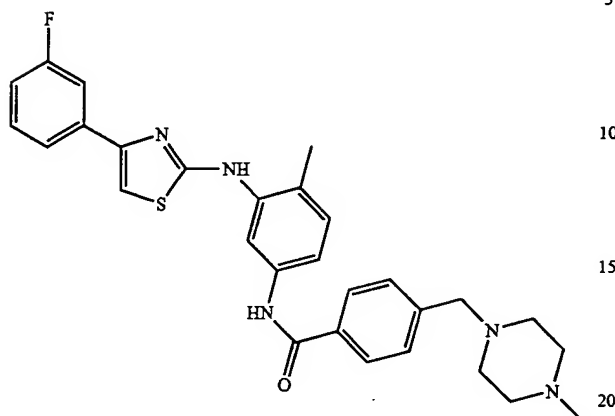
122: 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-2-yl-thiazol-2-ylamino)-phenyl]-benzamide



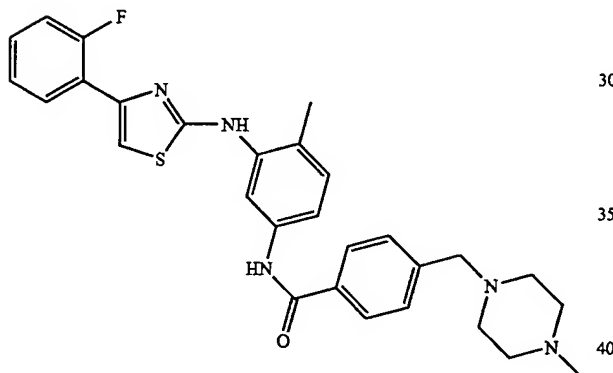


49

111: N-{3-[4-(3-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide

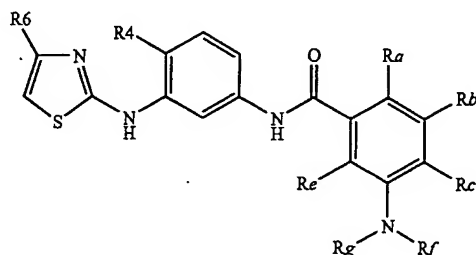


118: N-{3-[4-(2-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



Among compounds of formula II, the invention is particularly embodied by the compounds wherein X is a-aryl-substituted group, corresponding to the 3-Disubstituted-amino-N-[3-(thiazol-2-ylamino)-phenyl]-benzamide family and the following formula II-5:

FORMULA II-5



wherein Ra, Rb, Rc, Re, Rf, Rg are independently chosen from H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a

50

cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

or a NRR' group where R and R' are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or an OR group where R is H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; a —SO<sub>2</sub>-R' group wherein R' is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

or a NRaCORb group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a NRaCONRbRc group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

or a COOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom,

51

notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

or a CONRaRb, where Ra and Rb are a hydrogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

or an NHCOOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

an OSO<sub>2</sub>R, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

or an NRaOSO<sub>2</sub>Rb, where Ra and Rb are a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; Ra can also be a hydrogen; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

or a —SO<sub>2</sub>-R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a —CO—R or a —CO—NRR' group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at

52

least one heteroatom, notably selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality. Ra, Rb, Rc, Re can also be halogen such as Cl, F, Br, I or trifluoromethyl;

R<sup>4</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>6</sup> is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

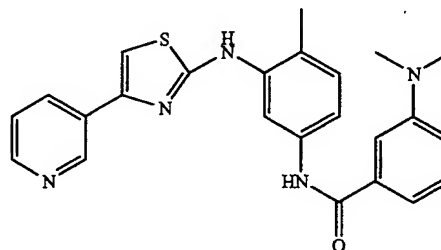
(ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

iv) H, a halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

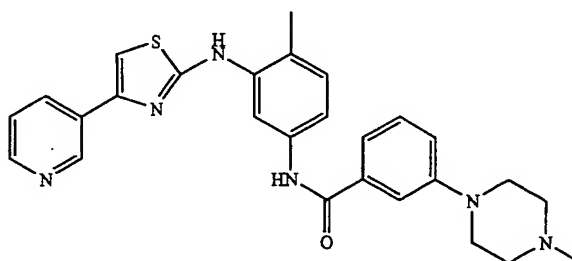
## EXAMPLES

088: 3-Dimethylamino-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



beige powder mp: 197-198° C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ=2.32 (s, 3H); 3.03 (s, 6H); 6.97 (d, J=6.4 Hz, 1H); 7.23-7.56 (m, 7H); 8.37 (d, J=7.3 Hz, 1H); 8.53 (d, J=4.7 Hz, 1H); 8.63 (s, 1H); 9.20 (s, 1H); 9.48 (s, 1H); 10.15 (s, 1H)

089: 3-(4-Methyl-piperazin-1-yl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

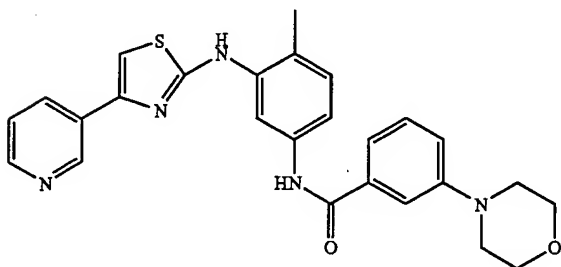


beige powder mp: 274-246° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>): δ=2.23 (s, 3H); 2.24-2.30 (m, 4H); 3.22-3.27 (m, 4H); 7.07-

53

7.20 (m, 2H); 7.36-7.53 (m, 6H); 8.31 (d, J=7.5 Hz, 1H); 8.47 (d, J=3.7 Hz, 1H) 8.58 (s, 1H); 9.12 (d, J=7.8 Hz, 1H); 9.44 (s, 1H); 10.12 (s, 1H)

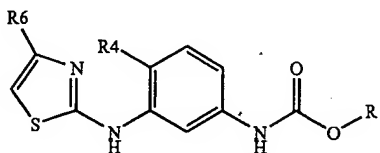
090: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-morpholin-4-yl-benzamide



beige powder mp: 247-248° C. <sup>1</sup>H RMN (CDCl<sub>3</sub>) δ=1.50 (s, 3H); 3.15-3.18 (m, 4H); 3.79-3.82 (m, 3H); 6.85 (s, 1H); 7.00-7.30 (m, 7H); 7.41 (s, 1H); 7.75 (s, 1H); 8.08 (d, J=7.9 Hz, 1H); 8.22 (d, J=1.7 Hz, 1H); 8.46 (dd, J=1.3 Hz, J=4.7 Hz, 1H); 9.01 (d, J=1.6 Hz, 1H)

Among the compounds of formula II, the invention is particularly embodied by the compounds wherein X is a —OR group, corresponding to the family [3-(Thiazol-2-ylamino)-phenyl]-carbamate and the following formula II-6

FORMULA II-6



wherein R is independently chosen from an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality;

R<sup>4</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>6</sup> is one of the following:

- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combi-

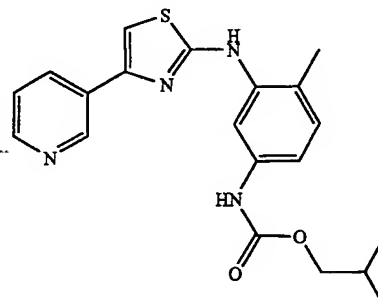
54

nation of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

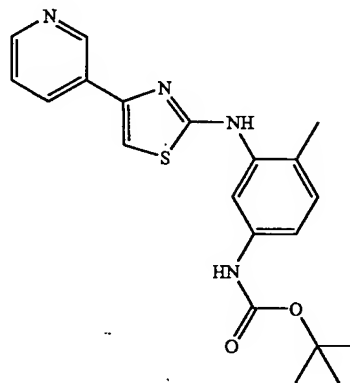
- iv) H, a halogen selected from I, F, Cl or Br, NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

## EXAMPLES

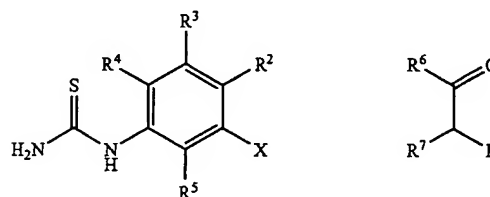
097: [4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-carbamic acid isobutyl ester



098: [4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-carbamic acid tert-butyl ester



In a second embodiment, the invention is directed to a process for manufacturing a compound of formula I depicted above. This entails the condensation of a substrate of general formula 10 with a thiourea of the type 11a-11d.



- 11 a: X = NH—R<sup>1</sup>
- 11 b: X = NH<sub>2</sub>
- 11 c: X = NH—PG
- 11 d: X = NO<sub>2</sub>

10

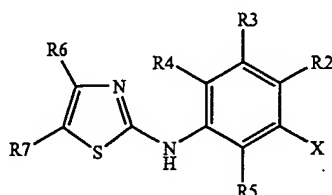
55

Substituent "L" in formula 10 is a leaving group suitable in nucleophilic substitution reactions (for example, L can be selected from chloro, bromo, iodo, toluenesulfonyloxy, methanesulfonyloxy, trifluoromethanesulfonyloxy, etc., with L being preferentially a bromo group).

Group R1 in formula 11a corresponds to group R1 as described in formula I.

Group "PG" in formula 11c is a suitable protecting group of a type commonly utilized by the person skilled in the art.

The reaction of 10 with 1 a-d leads to a thiozole-type product of formula 12a-d.



12 a: X = NH—R1  
12 b: X = NH2  
12 c: X = NH—PG  
12 d: X = NO2

Formula 12a is the same as formula I. Therefore, R1 in 12a corresponds to R1 in formula I.

Formula 12b describes a precursor to compounds of formula I which lack substituent R1. Therefore, in a second phase of the synthesis, substituent R1 is connected to the free amine group in 12b, leading to the complete structure embodied by formula I:

12b + "R1" → I

The introduction of R1, the nature of which is as described on page 3 for the general formula I, is achieved by the use of standard reactions that are well known to the person skilled in the art, such as alkylation, acylation, sulfonylation, formation of ureas, etc.

Formula 12c describes an N-protected variant of compound 12b. Group "PG" in formula 12c represents a protecting group of the type commonly utilized by the person skilled in the art. Therefore, in a second phase of the synthesis, group PG is cleaved to transform compound 12c into compound 12b. Compound 12b is subsequently advanced to structures of formula I as detailed above.

Formula 12d describes a nitro analogue of compound 12b. In a second phase of the synthesis, the nitro group of compound 12d is reduced by any of the several methods utilized by the person skilled in the art to produce the corresponding amino group, namely compound 12b. Compound 12b thus obtained is subsequently advanced to structures of formula I as detailed above.

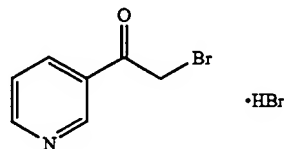
#### Examples of Compound Synthesis

General: All chemicals used were commercial reagent grade products. Dimethylformamide (DMF), methanol (MeOH) were of anhydrous commercial grade and were used without further purification. Dichloromethane and tetrahydrofuran (THF) were freshly distilled under a stream of argon before use. The progress of the reactions was monitored by thin layer chromatography using precoated silica gel 60F 254, Fluka TLC plates, which were visualized under UV light. Multiplicities in <sup>1</sup>H NMR spectra are indicated as singlet (s),

56

broad singlet (br s), doublet (d), triplet (t), quadruplet (q), and multiplet (m) and the NMR spectrum were realized on a 300 MHz Bruker spectrometer.

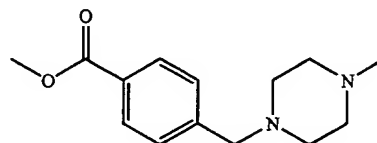
#### 3-Bromoacetyl-pyridine, HBr Salt



Dibromine (17.2 g, 108 mmol) was added dropwise to a cold (0° C.) solution of 3-acetyl-pyridine (12 g, 99 mmol) in acetic acid containing 33% of HBr (165 mL) under vigorous stirring. The vigorously stirred mixture was warmed to 40° C. for 2 h and then to 75° C. After 2 h at 75° C., the mixture was cooled and diluted with ether (400 mL) to precipitate the product, which was recovered by filtration and washed with ether and acetone to give white crystals (100%). This material may be recrystallised from methanol and ether.

IR (neat): 3108, 2047, 2982, 2559, 1709, 1603, 1221, 1035, 798 cm<sup>-1</sup>—<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ=5.09 (s, 2H, CH<sub>2</sub>Br); 7.88 (m, 1H, pyridyl-H); 8.63 (m, 1H, pyridyl-H); 8.96 (m, 1H, pyridyl-H); 9.29 (m, 1H, pyridyl-H).

#### Methyl-[4-(1-N-methyl-piperazino)-methyl]-benzoate

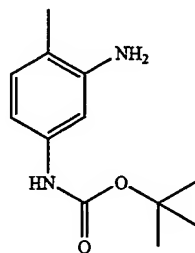


To methyl-4-formyl benzoate (4.92 g, 30 mmol) and N-methyl-piperazine (3.6 mL, 32 mmol) in acetonitrile (100 mL) was added dropwise 2.5 mL of trifluoroacetic acid. The reaction mixture was stirred at room temperature for 1 h. After slow addition of sodium cyanoborohydride (2 g, 32 mmol), the solution was left stirring overnight at room temperature. Water (10 mL) was then added to the mixture, which was further acidified with 1N HCl to pH=6-7. The acetonitrile was removed under reduced pressure and the residual aqueous solution was extracted with diethyl ether (4×30 mL). These extracts were discarded. The aqueous phase was then basified (pH>12) by addition of 2.5N aqueous sodium hydroxide solution. The crude product was extracted with ethyl acetate (4×30 mL). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated under reduced pressure to afford a slightly yellow oil which became colorless after purification by Kugelrohr distillation (190° C.) in 68% yield.

IR (neat): 3322, 2944, 2802, 1721, 1612, 1457, 1281, 1122, 1012—<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ=2.27 (s, 3H, NCH<sub>3</sub>); 2.44 (m, 8H, 2×NCH<sub>2</sub>CH<sub>2</sub>N); 3.53 (s, 2H, ArCH<sub>2</sub>N); 3.88 (s, 3H, OCH<sub>3</sub>); 7.40 (d, 2H, J=8.3 Hz, 2×ArH); 7.91 (d, 2H, J=8.3 Hz, 2×ArH)—<sup>13</sup>C NMR (CDCl<sub>3</sub>) δ=45.8 (NCH<sub>3</sub>); 51.8 (OCH<sub>3</sub>); 52.9 (2×CH<sub>2</sub>N); 54.9 (2×CH<sub>2</sub>N); 62.4 (ArCH<sub>2</sub>N); 128.7 (2×ArC); 129.3 (2×ArC); 143.7 (ArC); 166.7 (ArCO<sub>2</sub>CH<sub>3</sub>)-MS CI (m/z) (%) 249 (M+1, 100%).

57

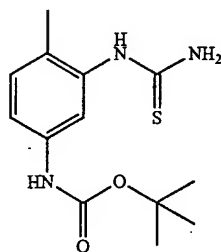
## 2-Methyl-5-tert-butoxycarbonylamino-aniline



A solution of di-tert-butyl dicarbonate (70 g, 320 mmol) in methanol (200 mL) was added over 2 h to a cold ( $-10^{\circ}\text{C}$ ) solution of 2,4-diaminotoluene (30 g, 245 mmol) and triethylamine (30 mL) in methanol (15 mL). The reaction was followed by thin layer chromatography (hexane/ethyl acetate, 3:1) and stopped after 4 h by adding 50 mL of water. The mixture was concentrated in vacuo and the residue was dissolved in 500 mL of ethyl acetate. This organic phase was washed with water (1x150 mL) and brine (2x150 mL), dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure. The resulting light brown solid was washed with small amounts of diethyl ether to give off-white crystals of 2-methyl-5-tert-butoxycarbonylamino-aniline in 67% yield.

IR (neat): 3359; 3246; 2970; 1719; 1609; 1557; 1173; 1050  $\text{cm}^{-1}$ — $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$ =1.50 (s, 9H, tBu); 2.10 (s, 3H,  $\text{ArCH}_3$ ); 3.61 (br s, 2H,  $\text{NH}_2$ ); 6.36 (br s, 1H, NH); 6.51 (dd, 1H,  $J$ =7.9 Hz, 2.3 Hz, ArH); 6.92 (d, 1H,  $J$ =7.9 Hz, ArH); 6.95 (s, 1H, ArH)— $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$ =16.6 ( $\text{ArCH}_3$ ); 28.3 ( $\text{C}(\text{CH}_3)_3$ ); 80.0 ( $\text{C}(\text{CH}_3)_3$ ); 105.2 (ArC); 108.6 (ArC); 116.9 (ArC); 130.4 ( $\text{ArC}-\text{CH}_3$ ); 137.2 ( $\text{ArC}-\text{NH}$ ); 145.0 ( $\text{ArC}-\text{NH}_2$ ); 152.8 ( $\text{COOtBu}$ ) MS ESI ( $m/z$ ) (%): 223 ( $M+1$ ), 167 (55, 100%).

## N-(2-methyl-5-tert-butoxycarbonylamino)phenyl-thiourea



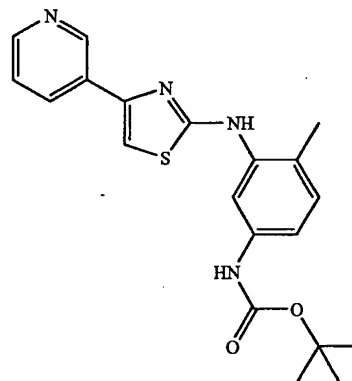
Benzoyl chloride (5.64 g, 80 mmol) was added dropwise to a well-stirred solution of ammonium thiocyanate (3.54 g, 88 mmol) in acetone (50 mL). The mixture was refluxed for 15 min, then, the hydrobromide salt of 2-methyl-5-tert-butoxycarbonylamino-aniline (8.4 g, 80 mmol) was added slowly portionswise. After 1 h, the reaction mixture was poured into ice-water (350 mL) and the bright yellow precipitate was isolated by filtration. This crude solid was then refluxed for 45 min in 70 mL of 2.5 N sodium hydroxide solution. The

58

mixture was cooled down and basified with ammonium hydroxide. The precipitate of crude thiourea was recovered by filtration and dissolved in 150 mL of ethyl acetate. The organic phase was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate, 1:1) to afford 63% of N-(2-methyl-5-tert-butoxycarbonylamino)phenyl-thiourea as a white solid.

IR (neat): 3437, 3292, 3175, 2983, 1724, 1616, 1522, 1161, 1053  $\text{cm}^{-1}$ — $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$ =1.46 (s, 9H, tBu); 2.10 (s, 3H,  $\text{ArCH}_3$ ); 3.60 (br s, 2H,  $\text{NH}_2$ ); 7.10 (d, 1H,  $J$ =8.29 Hz, ArH); 7.25 (d, 1H,  $J$ =2.23 Hz, ArH); 7.28 (d, 1H,  $J$ =2.63 Hz, ArH); 9.20 (s, 1H, ArNH); 9.31 (s, 1H, ArNH)— $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$ =25.1 ( $\text{ArCH}_3$ ); 28.1 ( $\text{C}(\text{CH}_3)_3$ ); 78.9 ( $\text{C}(\text{CH}_3)_3$ ); 16.6 (ArC); 117.5 (ArC); 128.0 (ArC); 130.4 ( $\text{ArC}-\text{CH}_3$ ); 136.5 ( $\text{ArC}-\text{NH}$ ); 137.9 ( $\text{ArC}-\text{NH}$ ); 152.7 ( $\text{COOtBu}$ ); 181.4 ( $\text{C}=\text{S}$ )—MS CI ( $m/z$ ): 282 ( $M+1$ , 100%); 248 (33); 226 (55); 182 (99); 148 (133); 93 (188).

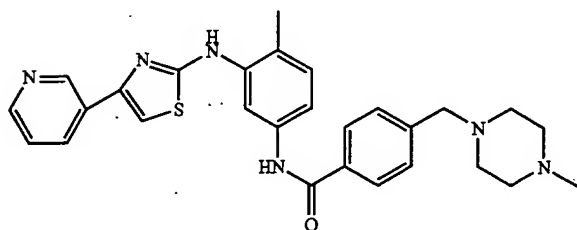
## 2-(2-methyl-5-tert-butoxycarbonylamino)phenyl-4-(3-pyridyl)-thiazole



A mixture of 3-bromoacetyl-pyridine, HBr salt (0.81 g, 2.85 mmol), N-(2-methyl-5-tert-butoxycarbonylamino)phenyl-thiourea (0.8 g, 2.85 mmol) and  $\text{KHCO}_3$  (~0.4 g) in ethanol (40 mL) was heated at  $75^{\circ}\text{C}$  for 20 h. The mixture was cooled, filtered (removal of  $\text{KHCO}_3$ ) and evaporated under reduced pressure. The residue was dissolved in  $\text{CHCl}_3$  (40 mL) and washed with saturated aqueous sodium hydrogen carbonate solution and with water. The organic layer was dried over  $\text{Na}_2\text{SO}_4$  and concentrated. Column chromatographic purification of the residue (hexane/ethyl acetate, 1:1) gave the desired thiazole in 70% yield as an orange solid.

IR (neat): 3380, 2985, 2942, 1748, 1447, 1374, 1239, 1047, 938  $\text{cm}^{-1}$ — $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$ =1.53 (s, 9H, tBu); 2.28 (s, 3H,  $\text{ArCH}_3$ ); 6.65 (s, 1H, thiazole-H); 6.89 (s, 1H); 6.99 (dd, 1H,  $J$ =8.3 Hz, 2.3 Hz); 7.12 (d, 2H,  $J$ =8.3 Hz); 7.35 (dd, 1H,  $J$ =2.6 Hz, 4.9 Hz); 8.03 (s, 1H); 8.19 (dt, 1H,  $J$ =1.9 Hz, 7.9 Hz); 8.54 (br s, 1H, NH); 9.09 (s, 1H, NH)— $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$ =18.02 ( $\text{ArCH}_3$ ); 29.2 ( $\text{C}(\text{CH}_3)_3$ ); 81.3 ( $\text{C}(\text{CH}_3)_3$ ); 104.2 (thiazole-C); 111.6; 115.2; 123.9; 124.3; 131.4; 132.1; 134.4; 139.5; 148.2; 149.1; 149.3; 153.6; 167.3 ( $\text{C}=\text{O}$ )—MS CI ( $m/z$ ) (%): 383 ( $M+1$ , 100%); 339 (43); 327 (55); 309 (73); 283 (99); 71 (311).

## 2-(2-methyl-5-amino)phenyl-4-(3-pyridyl)-thiazole



2-(2-methyl-5-tert-butoxycarbonylamino)phenyl-4-(3-pyridyl)-thiazole (0.40 g, 1.2 mmol) was dissolved in 10 mL of 20% TFA/CH<sub>2</sub>Cl<sub>2</sub>. The solution was stirred at room temperature for 2 h, then it was evaporated under reduced pressure. The residue was dissolved in ethyl acetate. The organic layer was washed with aqueous 1N sodium hydroxide solution, dried over MgSO<sub>4</sub>, and concentrated to afford 2-(2-methyl-5-amino)phenyl-4-(3-pyridyl)-thiazole as a yellow-orange solid in 95% yield. This crude product was used directly in the next step.

A 2M solution of trimethyl aluminium in toluene (2.75 mL) was added dropwise to a cold (0° C.) solution of 2-(2-methyl-5-amino)phenyl-4-(3-pyridyl)-thiazole (0.42 g, 1.5 mmol) in anhydrous dichloromethane (10 mL) under argon atmosphere. The mixture was warmed to room temperature and stirred at room temperature for 30 min. A solution of methyl-4-(1-N-methyl-piperazino)-methyl benzoate (0.45 g, 1.8 mmol) in anhydrous dichloromethane (1 mL) and added slowly, and the resulting mixture was heated at reflux for 5 h. The mixture was cooled to 0° C. and quenched by dropwise addition of a 4N aqueous sodium hydroxide solution (3 mL). The mixture was extracted with dichloromethane (3×20 mL). The combined organic layers were washed with brine (3×20 mL) and dried over anhydrous MgSO<sub>4</sub>. 2-(2-methyl-5-amino)phenyl-4-(3-pyridyl)-thiazole is obtained in 72% after purification by column chromatography (dichloromethane/methanol, 3:1)

IR (neat): 3318, 2926, 1647, 1610, 1535, 1492, 1282, 1207, 1160, 1011, 843—<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ=2.31 (br s, 6H, ArCH<sub>3</sub>+NCH<sub>3</sub>); 2.50 (br s, 8H, 2×NCH<sub>2</sub>CH<sub>2</sub>N); 3.56 (s, 2H, ArCH<sub>2</sub>N); 6.89 (s, 1H, thiazoleH); 7.21-7.38 (m, 4H); 7.45 (m, 2H); 7.85 (d, 2H, J=8.3 Hz); 8.03 (s, 1H); 8.13 (s, 1H); 8.27 (s, 1H); 8.52 (br s, 1H); 9.09 (s, 1H, NH)—<sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 17.8 (ArCH<sub>3</sub>); 46.2 (NCH<sub>3</sub>); 53.3 (NCH<sub>2</sub>); 55.3 (NCH<sub>2</sub>); 62.8 (ArCH<sub>2</sub>N); 99.9 (thiazole-C); 112.5; 123.9; 125.2; 127.5; 129.6; 131.6; 133.7; 134.0; 137.6; 139.3; 142.9; 148.8; 149.1; 166.2 (C=O); 166.7 (thiazoleC-NH)—MS CI (m/z) (%): 499 (M+H, 100%); 455 (43); 430 (68); 401 (97); 374 (124); 309 (189); 283 (215); 235 (263); 121 (377); 99 (399).

In a third embodiment, the invention relates to a pharmaceutical composition comprising a compound as depicted above.

Such medicament can take the form of a pharmaceutical composition adapted for oral administration, which can be formulated using pharmaceutically acceptable carriers well known in the art in suitable dosages. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient. In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries which facilitate pro-

cessing of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, Pa.).

The composition of the invention can also take the form of a pharmaceutical or cosmetic composition for topical administration.

Such compositions may be presented in the form of a gel, paste, ointment, cream, lotion, liquid suspension aqueous, aqueous-alcoholic or, oily solutions, or dispersions of the lotion or serum type, or anhydrous or lipophilic gels, or emulsions of liquid or semi-solid consistency of the milk type, obtained by dispersing a fatty phase in an aqueous phase or vice versa, or of suspensions or emulsions of soft, semi-solid consistency of the cream or gel type, or alternatively of microemulsions, of microcapsules, of microparticles or of vesicular dispersions to the ionic and/or nonionic type. These compositions are prepared according to standard methods.

The composition according to the invention comprises any ingredient commonly used in dermatology and cosmetic. It may comprise at least one ingredient selected from hydrophilic or lipophilic gelling agents, hydrophilic or lipophilic active agents, preservatives, emollients, viscosity enhancing polymers, humectants, surfactants, preservatives, antioxidants, solvents, and fillers, antioxidants, solvents, perfumes, fillers, screening agents, bactericides, odor absorbers and coloring matter.

As oils which can be used in the invention, mineral oils (liquid paraffin), vegetable oils (liquid fraction of shea butter, sunflower oil), animal oils, synthetic oils, silicone oils (cyclomethicone) and fluorinated oils may be mentioned. Fatty alcohols, fatty acids (stearic acid) and waxes (paraffin, carnauba, beeswax) may also be used as fatty substances.

As emulsifiers which can be used in the invention, glycerol stearate, polysorbate 60 and the PEG-6/PEG-32/glycol stearate mixture are contemplated.

As hydrophilic gelling agents, carboxyvinyl polymers (carbomer), acrylic copolymers such as acrylate/alkylacrylate copolymers, polyacrylamides, polysaccharides such as hydroxypropylcellulose, clays and natural gums may be mentioned, and as lipophilic gelling agents, modified clays such as bentonites, metal salts of fatty acids such as aluminum stearates and hydrophobic silica, or alternatively ethylcellulose and polyethylene may be mentioned.

As hydrophilic active agents, proteins or protein hydrolysates, amino acids, polyols, urea, allantoin, sugars and sugar derivatives, vitamins, starch and plant extracts, in particular those of Aloe vera may be used.

As lipophilic active agents, retinol (vitamin A) and its derivatives, tocopherol (vitamin E) and its derivatives, essential fatty acids, ceramides and essential oils may be used. These agents add extra moisturizing or skin softening features when utilized.

In addition, a surfactant can be included in the composition so as to provide deeper penetration of the compound capable of depleting mast cells, such as a tyrosine kinase inhibitor, preferably a c-kit inhibitor.

Among the contemplated ingredients, the invention embraces penetration enhancing agents selected for example from the group consisting of mineral oil, water, ethanol, triacetin, glycerin and propylene glycol; cohesion agents selected for example from the group consisting of polyisobutylene, polyvinyl acetate and polyvinyl alcohol, and thickening agents.

Chemical methods of enhancing topical absorption of drugs are well known in the art.

For example, compounds with penetration enhancing properties include sodium lauryl sulfate (Dugard, P. H. and Sheuplein, R. J., "Effects of Ionic Surfactants on the Permeability of Human Epidermis: An Electrometric Study," *J. Invest. Dermatol.*, V.60, pp. 263-69, 1973), lauryl amine oxide (Johnson et. al., U.S. Pat. No. 4,411,893), azone (Rajadhyaksha, U.S. Pat. Nos. 4,405,616 and 3,989,816) and decylmethyl sulfoxide (Sekura, D. L. and Scala, J., "The Percutaneous Absorption of Alkylmethyl Sulfides," *Pharmacology of the Skin, Advances In Biology of Skin*, (Appleton-Century Craft) V. 12, pp. 257-69, 1972). It has been observed that increasing the polarity of the head group in amphoteric molecules increases their penetration-enhancing properties but at the expense of increasing their skin irritating properties (Cooper, E. R. and Berner, B., "Interaction of Surfactants with Epidermal Tissues: Physicochemical Aspects," *Surfactant Science Series*, V. 16, Reiger, M. M. ed. (Marcel Dekker, Inc.) pp. 195-210, 1987).

A second class of chemical enhancers are generally referred to as co-solvents. These materials are absorbed topically relatively easily, and, by a variety of mechanisms, achieve permeation enhancement for some drugs. Ethanol (Gale et. al., U.S. Pat. No. 4,615,699 and Campbell et. al., U.S. Pat. Nos. 4,460,372 and 4,379,454), dimethyl sulfoxide (U.S. Pat. Nos. 3,740,420 and 3,743,727, and U.S. Pat. No. 4,575,515), and glycerine derivatives (U.S. Pat. No. 4,322,433) are a few examples of compounds which have shown an ability to enhance the absorption of various compounds.

The pharmaceutical compositions of the invention can also be intended for administration with aerosolized formulation to target areas of a patient's respiratory tract.

Devices and methodologies for delivering aerosolized bursts of a formulation of a drug is disclosed in U.S. Pat. No. 5,906,202. Formulations are preferably solutions, e.g. aqueous solutions, ethanoic solutions, aqueous/ethanoic solutions, saline solutions, colloidal suspensions and microcrystalline suspensions. For example aerosolized particles comprise the active ingredient mentioned above and a carrier, (e.g., a pharmaceutically active respiratory drug and carrier) which are formed upon forcing the formulation through a nozzle which nozzle is preferably in the form of a flexible porous membrane. The particles have a size which is sufficiently small such that when the particles are formed they remain suspended in the air for a sufficient amount of time such that the patient can inhale the particles into the patient's lungs.

The invention encompasses the systems described in U.S. Pat. No. 5,556,611:

liquid gas systems (a liquefied gas is used as propellant gas (e.g. low-boiling FCHC or propane, butane) in a pressure container,

suspension aerosol (the active substance particles are suspended in solid form in the liquid propellant phase),

pressurized gas system (a compressed gas such as nitrogen, carbon dioxide, dinitrogen monoxide, air is used.

Thus, according to the invention the pharmaceutical preparation is made in that the active substance is dissolved or dispersed in a suitable nontoxic medium and said solution or dispersion atomized to an aerosol, i.e. distributed extremely finely in a carrier gas. This is technically possible for example in the form of aerosol propellant gas packs, pump aerosols or other devices known per se for liquid misting and solid atomizing which in particular permit an exact individual dosage.

Therefore, the invention is also directed to aerosol devices comprising the compound as defined above and such a formulation, preferably with metered dose valves.

The pharmaceutical compositions of the invention can also be intended for intranasal administration.

In this regard, pharmaceutically acceptable carriers for administering the compound to the nasal mucosal surfaces will be readily appreciated by the ordinary artisan. These carriers are described in the Remington's *Pharmaceutical Sciences* 16th edition, 1980, Ed. By Arthur Osol, the disclosure of which is incorporated herein by reference.

The selection of appropriate carriers depends upon the particular type of administration that is contemplated. For administration via the upper respiratory tract, the composition can be formulated into a solution, e.g., water or isotonic saline, buffered or unbuffered, or as a suspension, for intranasal administration as drops or as a spray. Preferably, such solutions or suspensions are isotonic relative to nasal secretions and of about the same pH, ranging e.g., from about pH 4.0 to about pH 7.4 or, from pH 6.0 to pH 7.0. Buffers should be physiologically compatible and include, simply by way of example, phosphate buffers. For example, a representative nasal decongestant is described as being buffered to a pH of about 6.2 (Remington's, Id. at page 1445). Of course, the ordinary artisan can readily determine a suitable saline content and pH for an innocuous aqueous carrier for nasal and/or upper respiratory administration.

Common intranasal carriers include nasal gels, creams, pastes or ointments with a viscosity of, e.g., from about 10 to about 3000 cps, or from about 2500 to 6500 cps, or greater, may also be used to provide a more sustained contact with the nasal mucosal surfaces. Such carrier viscous formulations may be based upon, simply by way of example, alkylcelluloses and/or other biocompatible carriers of high viscosity well known to the art (see e.g., Remington's, cited supra. A preferred alkylcellulose is, e.g., methylcellulose in a concentration ranging from about 5 to about 1000 or more mg per 100 ml of carrier. A more preferred concentration of methyl cellulose is, simply by way of example, from about 25 to about mg per 100 ml of carrier.

Other ingredients, such as art known preservatives, colorants, lubricating or viscous mineral or vegetable oils, perfumes, natural or synthetic plant extracts such as aromatic oils, and humectants and viscosity enhancers such as, e.g., glycerol, can also be included to provide additional viscosity, moisture retention and a pleasant texture and odor for the formulation. For nasal administration of solutions or suspensions according to the invention, various devices are available in the art for the generation of drops, droplets and sprays.

A premeasured unit dosage dispenser including a dropper or spray device containing a solution or suspension for delivery as drops or as a spray is prepared containing one or more doses of the drug to be administered and is another object of the invention. The invention also includes a kit containing one or more unit dehydrated doses of the compound, together with any required salts and/or buffer agents, preservatives, colorants and the like, ready for preparation of a solution or suspension by the addition of a suitable amount of water.

Another aspect of the invention is directed to the use of said compound to manufacture a medicament. In other words, the invention embraces a method for treating a disease related to unregulated c-kit transduction comprising administering an effective amount of a compound as defined above to a mammal in need of such treatment.

More particularly, the invention is aimed at a method for treating a disease selected from autoimmune diseases, allergic diseases, bone loss, cancers such as leukemia and GIST, tumor angiogenesis, inflammatory diseases, inflammatory bowel diseases (IBD), interstitial cystitis, mastocytosis, infections diseases, metabolic disorders, fibrosis, diabetes



and CNS disorders comprising administering an effective amount of a compound depicted above to a mammal in need of such treatment.

The above described compounds are useful for manufacturing a medicament for the treatment of diseases related to unregulated c-kit transduction, including, but not limited to:

neoplastic diseases such as mastocytosis, canine mastocytoma, human gastrointestinal stromal tumor ("GIST"), small cell lung cancer, non-small cell lung cancer, acute myelocytic leukemia, acute lymphocytic leukemia, myelodysplastic syndrome, chronic myelogenous leukemia, colorectal carcinomas, gastric carcinomas, gastrointestinal stromal tumors, testicular cancers, glioblastomas, solid tumors and astrocytomas.

tumor angiogenesis.

metabolic diseases such as diabetes mellitus and its chronic complications; obesity; diabetes type II; hyperlipidemias and dyslipidemias; atherosclerosis; hypertension; and cardiovascular disease.

allergic diseases such as asthma, allergic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, angioedema, atopic dermatitis, allergic contact dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing vasculitis and insect bite skin inflammation and blood sucking parasitic infestation.

interstitial cystitis.

bone loss (osteoporosis).

inflammatory diseases such as rheumatoid arthritis, conjunctivitis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions.

autoimmune diseases such as multiple sclerosis, psoriasis, intestine inflammatory disease, ulcerative colitis, Crohn's disease, rheumatoid arthritis and polyarthritis, local and systemic scleroderma, systemic lupus erythematosus, discoid lupus erythematosus, cutaneous lupus, dermatomyositis, polymyositis, Sjogren's syndrome, nodular panarteritis, autoimmune enteropathy, as well as proliferative glomerulonephritis.

graft-versus-host disease or graft rejection in any organ transplantation including kidney, pancreas, liver, heart, lung, and bone marrow.

Other autoimmune diseases embraced by the invention active chronic hepatitis and chronic fatigue syndrome subepidermal blistering disorders such as pemphigus.

Vasculitis.

melanocyte dysfunction associated diseases such as hypermelanosis resulting from melanocyte dysfunction and including lentigines, solar and senile lentigo, Dubreuilh melanosis, moles as well as malignant melanomas. In this regard, the invention embraces the use of the compounds defined above to manufacture a medicament or a cosmetic composition for whitening human skin.

CNS disorders such as psychiatric disorders, migraine, pain, memory loss and nerve cells degeneracy. More particularly, the method according to the invention is useful for the treatment of the following disorders: Depression including dysthymic disorder, cyclothymic disorder, bipolar depression, severe or "melancholic" depression, a typical depression, refractory depression, seasonal depression, anorexia, bulimia, premenstrual syndrome, post-menopause syndrome, other syndromes such as mental slowing and loss of concentration, pessimistic worry, agitation, self-deprecation, decreased libido, pain including, acute pain, postoperative pain, chronic pain, nociceptive pain, cancer pain, neuropathic pain, psychogenic pain syndromes, anxiety disorders including anxiety associated with hyperventilation and

cardiac arrhythmias, phobic disorders, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, psychiatric emergencies such as panic attacks, including psychosis, delusional disorders, conversion disorders, phobias, mania, delirium, dissociative episodes including dissociative amnesia, dissociative fugue and dissociative identity disorder, depersonalization, catatonia, seizures, severe psychiatric emergencies including suicidal behaviour, self-neglect, violent or aggressive behaviour, trauma, borderline personality, and acute psychosis, schizophrenia including paranoid schizophrenia, disorganized schizophrenia, catatonic schizophrenia, and undifferentiated schizophrenia,

neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, Huntington's disease, the prion diseases, Motor Neurone Disease (MND), and Amyotrophic Lateral Sclerosis (ALS).

substance use disorders as referred herein include but are not limited to drug addiction, drug abuse, drug habituation, drug dependence, withdrawal syndrome and overdose.

Cerebral ischemia

Fibrosis

Duchenne muscular dystrophy

Regarding mastocytosis, the invention contemplates the use of the compounds as defined above for treating the different categories which can be classified as follows:

The category I is composed by two sub-categories (IA and IB). Category IA is made by diseases in which mast cell infiltration is strictly localized to the skin. This category represents the most frequent form of the disease and includes: i) urticaria pigmentosa, the most common form of cutaneous mastocytosis, particularly encountered in children, ii) diffuse cutaneous mastocytosis, iii) solitary mastocytoma and iv) some rare subtypes like bullous, erythrodermic and teleangiectatic mastocytosis. These forms are characterized by their excellent prognosis with spontaneous remissions in children and a very indolent course in adults. Long term survival of this form of disease is generally comparable to that of the normal population and the translation into another form of mastocytosis is rare. Category IB is represented by indolent systemic disease (SM) with or without cutaneous involvement. These forms are much more usual in adults than in children. The course of the disease is often indolent, but sometimes signs of aggressive or malignant mastocytosis can occur, leading to progressive impaired organ function.

The category II includes mastocytosis with an associated hematological disorder, such as a myeloproliferative or myelodysplastic syndrome, or acute leukemia. These malignant mastocytosis does not usually involve the skin. The progression of the disease depends generally on the type of associated hematological disorder that conditions the prognosis.

The category III is represented by aggressive systemic mastocytosis in which massive infiltration of multiple organs by abnormal mast cells is common. In patients who pursue this kind of aggressive clinical course, peripheral blood features suggestive of a myeloproliferative disorder are more prominent. The progression of the disease can be very rapid, similar to acute leukemia, or some patients can show a longer survival time.

Finally, the category IV of mastocytosis includes the mast cell leukemia, characterized by the presence of circulating mast cells and mast cell progenitors representing more than 10% of the white blood cells. This entity represents probably the rarest type of leukemia in humans, and has a very poor



prognosis, similar to the rapidly progressing variant of malignant mastocytosis. Mast cell leukemia can occur either de novo or as the terminal phase of urticaria pigmentosa or systemic mastocytosis.

The invention also contemplates the method as depicted for the treatment of recurrent bacterial infections, resurging infections after asymptomatic periods such as bacterial cystitis. More particularly, the invention can be practiced for treating FimH expressing bacteria infections such as Gram-negative enterobacteria including *E. coli*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Citrobacter freundii* and *Salmonella typhimurium*. In this method for treating bacterial infection, separate, sequential or concomitant administration of at least one antibiotic selected bacitracin, the cephalosporins, the penicillins, the aminoglycosides, the tetracyclines, the streptomycins and the macrolide antibiotics such as erythromycin; the fluoroquinolones, actinomycin, the sulfonamides and trimethoprim, is of interest.

In one preferred embodiment, the invention is directed to a method for treating neoplastic diseases such as mastocytosis, canine mastocytoma, human gastrointestinal stromal tumor ("GIST"), small cell lung cancer, non-small cell lung cancer, acute myelocytic leukemia, acute lymphocytic leukemia, myelodysplastic syndrome, chronic myelogenous leukemia, colorectal carcinomas, gastric carcinomas, gastrointestinal stromal tumors, testicular cancers, glioblastomas, and astrocytomas comprising administering a compound as defined herein to a human or mammal, especially dogs and cats, in need of such treatment.

In one other preferred embodiment, the invention is directed to a method for treating allergic diseases such as asthma, allergic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, angioedema, atopic dermatitis, allergic contact dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing vasculitis and insect bite skin inflammation and blood sucking parasitic infestation comprising administering a compound as defined herein to a human or mammal, especially dogs and cats, in need of such treatment.

In still another preferred embodiment, the invention is directed to a method for treating inflammatory diseases such as rheumatoid arthritis, conjunctivitis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions comprising administering a compound as defined herein to a human in need of such treatment.

In still another preferred embodiment, the invention is directed to a method for treating autoimmune diseases such as multiple sclerosis, psoriasis, intestine inflammatory disease, ulcerative colitis, Crohn's disease, rheumatoid arthritis and polyarthritis, local and systemic scleroderma, systemic lupus erythematosus, discoid lupus erythematosus, cutaneous lupus, dermatomyositis, polymyositis, Sjogren's syndrome, nodular panarteritis, autoimmune enteropathy, as well as proliferative glomerulonephritis comprising administering a compound as defined herein to a human in need of such treatment.

In still another preferred embodiment, the invention is directed to a method for treating graft-versus-host disease or graft rejection in any organ transplantation including kidney, pancreas, liver, heart, lung, and bone marrow comprising administering a compound as defined herein to a human in need of such treatment.

## In Vitro TK Inhibition Assays

## Procedure

Experiments were performed using purified intracellular domain of c-kit expressed in baculovirus. Estimation of the kinase activity was assessed by the phosphorylation of tyrosine containing target peptide estimated by established ELISA assay.

## Experimental Results on Tested Compounds

Result in Table 1 shows the potent inhibitory action of the catalytic activity of c-kit with an IC<sub>50</sub><10  $\mu$ M. Further experiments (not shown) indicates that at least one compound acts as perfect competitive inhibitors of ATP.

TABLE 1

Compounds	In vitro Inhibition assay results c-kit IC <sub>50</sub> ( $\mu$ M)
066; 074; 078; 084; 012; 016; 073; 021; 088; 023; 025; 047; 048; 055; 049; 026; 087; 075; 089; 051; 082; 090; 060; 085; 052; 053; 096	<10 $\mu$ M

## Example 2

## Ex Vivo TK Inhibition Assays

## Procedures

## C-Kit WT and Mutated C-Kit (JM) Assay

## Proliferation Assays

Cells were washed two times in PBS before plating at  $5 \times 10^4$  cells per well of 96-well plates in triplicate and stimulated either with hematopoietic growth factors (HGF) or without. After 2 days of culture, 37 Bq (1.78 Tbq/mmol) of [<sup>3</sup>H] thymidine (Amersham Life Science, UK) was added for 6 hours. Cells were harvested and filtered through glass fiber filters and [<sup>3</sup>H] thymidine incorporation was measured in a scintillation counter. For proliferation assay, all drugs were prepared as 20 mM stock solutions in DMSO and conserved at -80° C. Fresh dilutions in PBS were made before each experiment. DMSO dissolved drugs were added at the beginning of the culture. Control cultures were done with corresponding DMSO dilutions. Results are represented in percentage by taking the proliferation without inhibitor as 100%.

## Cells

Ba/F3 murine kit and human kit, Ba/F3 mkitA27 (juxtamembrane deletion) are derived from the murine IL-3 dependent Ba/F3 proB lymphoid cells. The FMA3 and P815 cell lines are mastocytoma cells expressing endogenous mutated forms of Kit, i.e., frame deletion in the murine juxtamembrane coding region of the receptor-codons 573 to 579. The human leukaemic MC line HMC-1 expresses mutations JM-V560G;

## Immunoprecipitation Assays and Western Blotting Analysis

For each assay,  $5.10^6$  Ba/F3 cells and Ba/F3-derived cells with various c-kit mutations were lysed and immunoprecipitated as described (Beslu et al., 1996), excepted that cells were stimulated with 250 ng/ml of rmKL. Cell lysates were immunoprecipitated with a rabbit immunoserum anti murine KIT, directed against the KIT cytoplasmic domain (Rottapel

67

et al., 1991). Western blot was hybridized either with the 4G10 anti-phosphotyrosine antibody (UBI) or with the rabbit immunoserum anti-murine KIT or with different antibodies (described in antibodies paragraph). The membrane was then incubated either with HRP-conjugated goat anti mouse IgG antibody or with HRP-conjugated goat anti rabbit IgG antibody (Immunotech). Proteins of interest were then visualized by incubation with ECL reagent (Amersham).

#### Experimental Results

The experimental results for various compounds according to the invention using above-described protocols are set forth at Table 2:

TABLE 2

Target	IC50 ( $\mu$ M)	Compounds
c-Kit WT	IC50 <10 $\mu$ M	002; 005; 006; 007; 008; 009; 010; 012; 017; 019; 020; 021; 023; 024; 025; 026; 028; 029; 030; 032; 042; 043; 045; 047; 048; 049; 050; 051; 052; 053; 054; 055; 056; 057; 059; 060; 061; 062; 063; 064; 065; 066; 067; 072; 073; 074; 075; 077; 078; 079; 080; 081; 082; 083; 084; 085; 086; 087; 088; 089; 090; 092; 093; 094; 095; 096; 097; 106; 105; 104; 103; 128; 129; 130; 131; 117; 110; 116; 124; 108; 122; 111; 113; 118; 107;
c-Kit JM $\Delta$ 27	IC50 <1 $\mu$ M	028; 074; 029; 009; 012; 073; 020; 042; 061; 065; 088; 025; 048; 049; 050; 089; 051; 082; 090; 083; 059; 052; 053; 066; 103; 067; 104; 078; 079; 105; 081; 084; 030; 010; 021; 043; 054; 062; 106; 023; 024; 064; 047; 055; 026; 087; 075; 085; 005; 077; 092; 060; 032; 017; 063; 093; 094; 095; 086; 093; 096; 108; 117; 122; 008; 080; 111; 118; 113; 007; 072; 019; 056; 057; 107; 097;

#### Example 3

##### In Vivo Activity

##### Procedures

##### GIST

cells: Ba/F3 cells were transfected by c-kit gene having  $\Delta$ 27 mutation (GIST model). Ba/F3 expressing the mutated c-kit gene readily proliferate in the absence of IL3 or SCF and are tumorigenic in nude mice.

##### Protocol:

Mice were irradiated at J-1 (5Gy)

Tumor cells ( $10^6$ ) were subcutaneously grafted at Jo

Tumor size were daily measured from J14

Number of survival mice were daily estimated

In this experimental model, the tumor size at J14 is about 20 mm<sup>3</sup>

Treated mice received per os twice a day a dose of 100 mg/kg of one compound of formula II-3 during 5 days (from J26 to J30).

##### Rheumatoid Arthritis

The mice were pretreated with the compound of formula II-3 (2x, 12.5 mg/kg) for two days (day-2, day-1) before induction of arthritis. Arthritis was induced by ip injection of 150- $\mu$ l serums at days 0 and 2. The treatment with the compound (2x, 12.5 mg/kg) was continued for 14 days. The control mice were injected with, 1% PBS before the induction of arthritis and during the course of the disease. Ankle thickness and arthritis score was evaluated for 15 days. Arthritis Score: 5  $\mu$ m of scores of each limb (0 no disease; 1 mild swelling of paw or of just a few digits; 2 clear joint inflammation; 3 severe joint inflammation) maximum score=12. Table 3A and Table 3B show the number of mice used in this

68

study. Two sets of experiments were done with different number of mice, one with 4 mices the other with 8 mices.

TABLE 3A

Treated Mice 2x, 12.5 mg/Kg	C57B1/6 6
--------------------------------	--------------

TABLE 3B

Controls 2X, 1% PBS	C57B1/6 6
------------------------	--------------

##### Histology

At the end of the experiment the hind limbs were collected. The skin of the limb was removed and the limbs were subsequently fixed in 2% Para formaldehyde.

##### Experimental Results

##### GIST

Treated mice (with one compound of formula II-3) displays significant decrease of tumor size at J30 and J33 compared to control.

##### 25 When administrated per os, one tested compound of the formula II-3 displays a significant antitumor activity against tumors cells expressing c-kit A27.

##### RA

A compound of the formula II-3 has demonstrated significant activity in the in vivo mouse model of arthritis. Results are shown on FIGS. 1, 2, 3, 4.

#### BRIEF DESCRIPTION OF DRAWINGS

FIG. 1: Effect of the compound in serum transfer experiments, Protocol, ip daily treatment with the compound (2x12.5 mg/kg) and on days-2 and -1, set of experiment with 4 mices (T: treated, C: control)

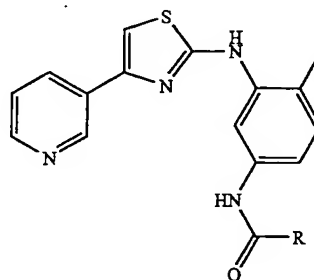
FIG. 2: Effect of the compound in serum transfer experiments, Protocol, ip daily treatment with the compound (2x12.5 mg/kg) and on days-2 and -1, set of experiment with 4 mices (T: treated, C: control)

FIG. 3: Effect of the compound in serum transfer experiments, Protocol, ip daily treatment with the compound (2x12.5 mg/kg) and on days -2 and -1, set of experiment with 8 mices (T: treated, C: control)

FIG. 4: Effect of the compound in serum transfer experiments, Protocol, ip daily treatment with the compound (2x12.5 mg/kg) and on days-2 and -1, set of experiment with 8 mices (T: treated, C: control)

The invention claimed is:

1. A compound according to the following formula:



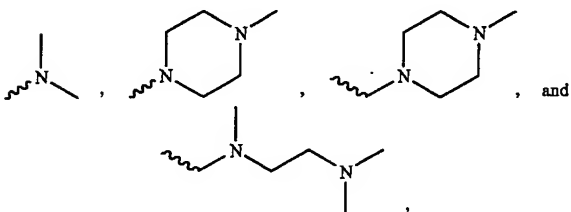
69

wherein R is:

H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality; or

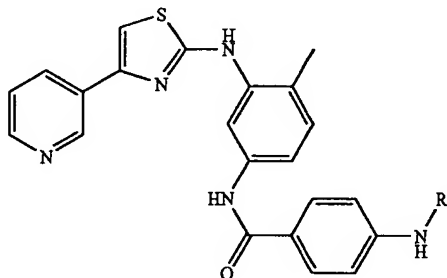
a cycloalkyl, an aryl or heteroaryl group optionally substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

wherein said pendant basic nitrogen functionality is selected from the group consisting of



wherein the wavy line corresponds to the point of attachment.

2. A compound according to the following formula:



wherein R is:

H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality; or

a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one substituent selected from I, Cl, Br, F, and a pendant basic nitrogen functionality; or

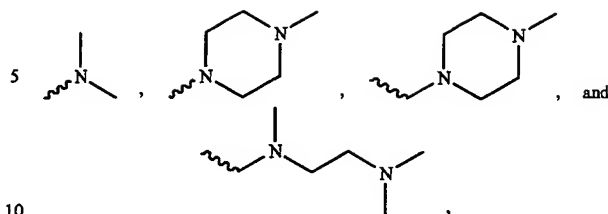
a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one substituent selected from I, Cl, Br, F, and a pendant basic nitrogen functionality; or

a —SO<sub>2</sub>-R" group wherein R" is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality; or

a —CO-R' or —CO-NR'R" group, wherein R' and R" are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

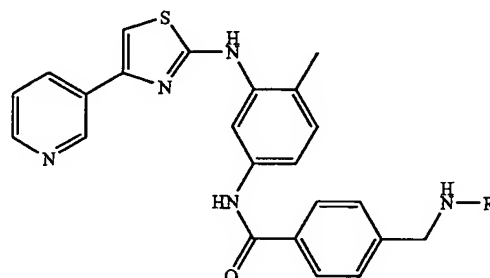
wherein said pendant basic nitrogen functionality is selected from the group consisting of

70



wherein the wavy line corresponds to the point of attachment.

3. A compound according to the following formula:



wherein R is H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

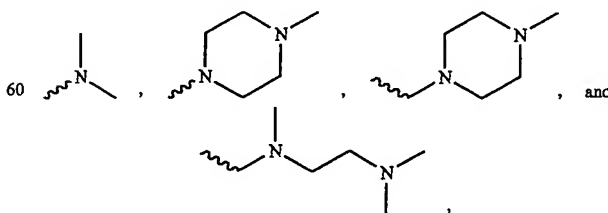
a cycloalkyl, aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

an alkyl, cycloalkyl, aryl or heteroaryl group substituted by a alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

a —SO<sub>2</sub>-R" group wherein R" is an alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

a —CO-R' or a —CO-NR'R" group, wherein R' and R" are independently chosen from H or an aryl heteroaryl, alkyl and cycloalkyl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

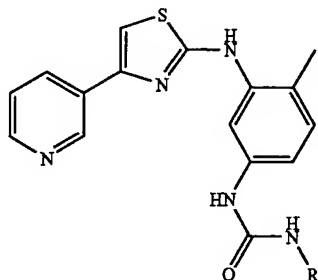
wherein said pendant basic nitrogen functionality is selected from the group consisting of



wherein the wavy line corresponds to the point of attachment.

71

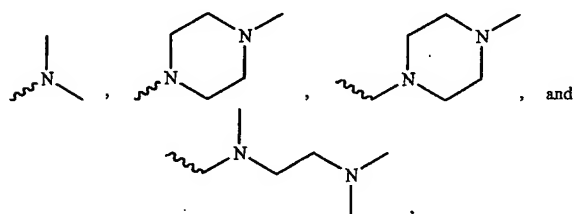
4. A compound according to of the following formula:



wherein R is:

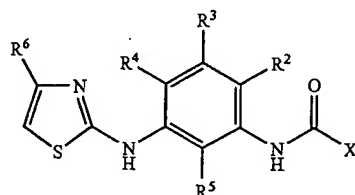
H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

wherein said pendant basic nitrogen functionality is selected from the group consisting of



wherein the wavy line corresponds to the point of attachment.

5. A compound according to formula II:

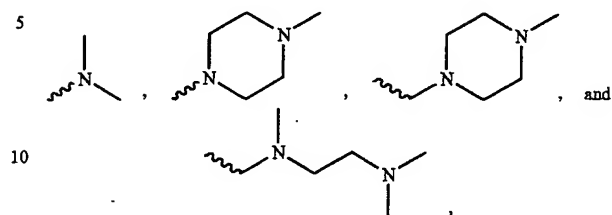


FORMULA II

wherein X is R or NRR' and wherein R and R' are independently chosen from H, an aryl, an heteroaryl, an alkyl and a cycloalkyl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality; an aryl, an heteroaryl, an alkyl and a cycloalkyl group substituted with an aryl, an heteroaryl, an alkyl and a cycloalkyl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

72

wherein said pendant basic nitrogen functionality is selected from the group consisting of



wherein the wavy line corresponds to the point of attachment;

R<sup>2</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>3</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>4</sup> is halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>5</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>6</sup> is one of the following:

- (i) an aryl group optionally substituted by one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, or alkoxy;
- (ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear one or more substituents;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl, which may additionally bear one or more substituents.

6. A compound according to claim 5 selected from the group consisting of:

1-(4-Bromo-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 010);

1-(4-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 012);

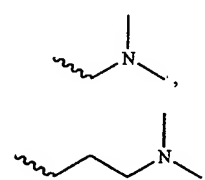
1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-thiophen-2-yl-urea (example 015);

1-(3,5-Dimethyl-isoxazol-4-yl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 019);

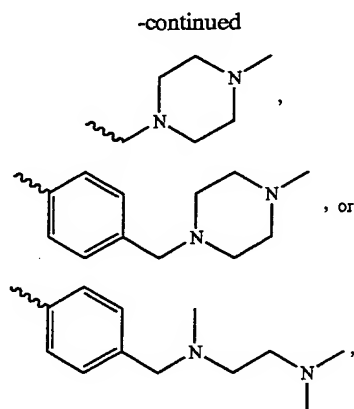
1-(2-Iodo-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 020); and

1-(4-Dimethylamino-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 022).

7. A compound according to claim 5, wherein X is selected from the structures (a)-(d) and (f) shown below:



73



wherein the wavy line corresponds to the point of attachment to core structure of formula II.

8. A compound according to claim 7, wherein X is group (d) and R<sup>6</sup> is a 3-pyridyl group.

9. A compound according to claim 7, wherein X is group (d) and R<sup>4</sup> is a methyl group.

10. A compound according to claim 7, wherein X is group (d) and R<sup>2</sup> and/or R<sup>3</sup> and/or R<sup>5</sup> is H.

11. The compound of claim 5 which is: 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-4-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 080).

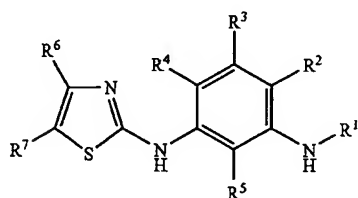
12. A compound which is: N-{3-[4-(4-cyano-phenyl)-thiazol-2-ylamino]}-4-methyl-phenyl-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 081).

13. The compound of claim 5 which is: 4-(4-methyl-piperazin-1-yl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 060) or 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 066).

14. A compound which is: 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 066).

15. A composition comprising a compound of claim 14 and a pharmaceutically acceptable carrier.

16. A compound of formula I:



wherein R<sup>1</sup> is:

—C(O)R, —C(O)OR, or —CO—NRR', wherein R and R' are independently selected from the group consisting of hydrogen, aryl, heteroaryl, alkyl, and cycloalkyl, each optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality;

R<sup>2</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

74

R<sup>3</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>4</sup> is halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>5</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>6</sup> is one of the following:

(i) an aryl group such as phenyl optionally substituted by one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, or alkoxy;

(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear one or more substituents; or

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl, which may additionally bear one or more substituents;

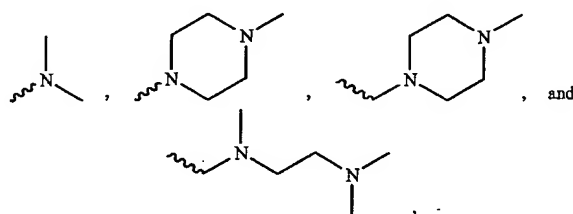
and R<sup>7</sup> is one of the following:

(i) an aryl group such as phenyl optionally substituted by one or more substituents;

(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear one or more substituents;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl, which may additionally bear one or more substituents; or

(iv) H, a halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> and SO<sub>2</sub>—R", wherein R" is a linear or branched alkyl group optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality; wherein said pendant basic nitrogen functionality is selected from the group consisting of

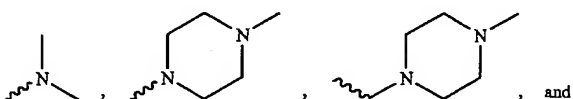


wherein the wavy line corresponds to the point of attachment.

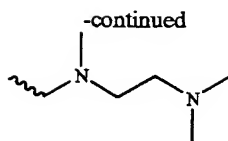
17. A composition comprising a compound of claim 16 in a pharmaceutically acceptable carrier.

18. A compound according to claim 16, wherein R<sup>1</sup> is

—C(O)R, wherein R is independently selected from the group consisting of hydrogen, aryl, heteroaryl, alkyl, and cycloalkyl, each optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality; wherein said pendant basic nitrogen functionality is selected from the group consisting of



75



wherein the wavy line corresponds to the point of attachment.

19. A compound according to claim 18 selected from the group consisting of:

- N-[4-Methyl-3-(4-phenyl-thiazol-2-ylamino)-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 004);
- N-[3-[(2,4')Bithiazolyl-2'-ylamino]-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide; (example 005);
- N-[4-Chloro-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 027);
- 3-Bromo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 028);
- 3-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 029);
- 2-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 032);
- 4-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 033);
- 3-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 045);
- 4-Dimethylamino-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 047);
- 4-(4-Methyl-piperazin-1-yl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-benzamide (example 060);
- N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-isonicotinamide (example 063);
- 2,6-Dichloro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-isonicotinamide (example 064);
- 3,5-Dibromo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 067);
- 3-Fluoro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 074);
- 2,3,5,6-Tetrafluoro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 076);
- N-[3-[4-(4-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 077);
- 3-Bromo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 078);
- 3-Chloro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 079);
- N-[4-Methyl-3-[4-(5-methyl-pyridin-3-yl)-thiazol-2-ylamino)-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 084);
- 3-Iodo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 085);
- 3-Dimethylamino-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 088);

76

3-(4-Methyl-piperazin-1-yl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 089);

Cyclohexanecarboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide (example 092);

5-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-pentanoic acid ethyl ester (example 093);

4-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 104);

N-[3-[4-(4-Chloro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 108);

N-[3-[4-(4-Methoxy-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 110);

N-[3-[4-(3-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 111);

N-[3-[4-(3-Methoxy-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 113);

4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-[4-(3-trifluoromethyl-phenyl)-thiazol-2-ylamino]-phenyl]-benzamide (example 116);

N-[3-[4-(2-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 118);

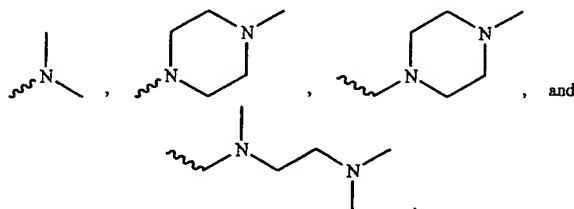
4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-2-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 122); and

N-[3-[4-(2,5-Dimethyl-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 124).

20. A pharmaceutical composition comprising a compound according to claim 18 and a pharmaceutically acceptable carrier.

21. A compound according to claim 16, wherein R' is —CO—NRR', wherein R and R' are independently selected from the group consisting of hydrogen, aryl, heteroaryl, alkyl, and cycloalkyl, each optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality;

wherein said pendant basic nitrogen functionality is selected from the group consisting of



wherein the wavy line corresponds to the point of attachment.

22. A compound according to claim 21 selected from the group consisting of:

1-(2-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 023);

1-(2-Chloro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 024); and

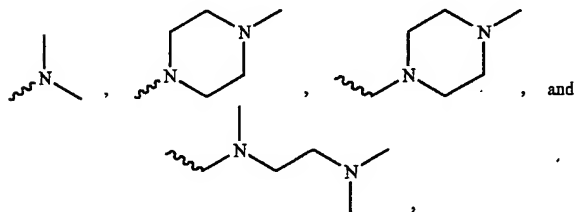
1-(3-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 025).

77

23. A pharmaceutical composition comprising a compound according to claim 21 and a pharmaceutically acceptable carrier.

24. A compound according to claim 16, wherein R' is

—C(O)OR, wherein R is selected from the group consisting of hydrogen, aryl, heteroaryl, alkyl, and cycloalkyl, each optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality; wherein said pendant basic nitrogen functionality is selected from the group consisting of



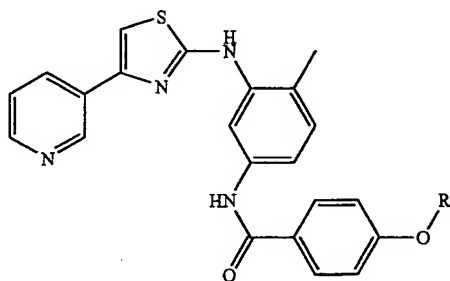
wherein the wavy line corresponds to the point of attachment.

25. A compound according to claim 24 selected from the group consisting of:

[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-carbamic acid isobutyl ester (example 097), and [4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-carbamic acid tert-butyl ester (example 098).

26. A pharmaceutical composition comprising a compound according to claim 25 and a pharmaceutically acceptable carrier.

27. A compound according to the following formula:



wherein R is H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom, or bearing at least one pendant basic nitrogen functionality;

a cycloalkyl, aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality; or

an alkyl, cycloalkyl, aryl or heteroaryl group substituted by a alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality; or

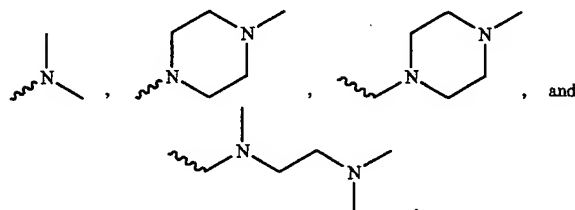
a —SO<sub>2</sub>-R'' group wherein R'' is an alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

a —CO—R' or a —CO—NR'R''—group wherein R' and R'' are independently chosen from H or an aryl het-

78

eroaryl, alkyl and cycloalkyl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

wherein said pendant basic nitrogen functionality is selected from the group consisting of selected from the group consisting of



wherein the wavy line corresponds to the point of attachment.

28. A compound according to claim 27 selected from the group consisting of

4-Hydroxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 037);

Thiophene-2-sulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester (example 042);

4-Iodo-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester (example 043);

4-Isopropoxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 050);

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(2-morpholin-4-yl-ethoxy)-benzamide (example 052);

3-Fluoro-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester (example 056);

2-Fluoro-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester (example 058); and

3-Methoxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 059).

29. A compound according to claim 2 selected from the group consisting of

4-[3-(4-Bromo-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 036);

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-(3-thiophen-2-yl-ureido)-benzamide (example 038);

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-(thiophene-2-sulfonylamino)-benzamide (example 044);

4-[3-(2-Iodo-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 101); and

4-[3-(4-Fluoro-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 102).

30. A compound selected from the group consisting of 1-(4-Methoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 009);

1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(4-trifluoromethyl-phenyl)-urea (example 011);

1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(3,4,5-trimethoxy-phenyl)-urea (example 013);

4-{3-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-ureido}-benzoic acid ethyl ester (example 014);  
 1-Cyclohexyl-1-(N-Cyclohexyl-formamide)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 016);  
 1-(2,4-Dimethoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 017);  
 1-(2-Iodo-phenyl)-1-(N-(2-Iodo-phenyl)-formamide)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 018);  
 1-(4-Difluoromethoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 021);  
 1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-p-tolyl-urea (example 026);  
 (4-Hydroxymethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 030);  
 4-(3-{4-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]carbamoyl}-phenyl)-ureido)-benzoic acid ethyl ester (example 034);  
 N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide (example 035);  
 4-[3-(3,5-Dimethyl-isoxazol-4-yl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 039);  
 4-[3-(4-Methoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 040);  
 4-[3-(4-Difluoromethoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 041);  
 2-Fluoro-5-methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 048);  
 4-tert-Butyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 049);

Benzo [1,3]dioxole-5-carboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide (example 051);  
 3-Cyano-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 054);  
 2-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide (example 055);  
 3-Methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 061);  
 Biphenyl-3-carboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide (example 062);  
 N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide (example 065);  
 {4-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]carbamoyl}-benzyl]-carbamic acid tert-butyl ester (example 073);  
 3-Fluoro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 074);  
 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide (example 075);  
 4-(1-Methoxy-ethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 083);  
 N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[3-(4-trifluoromethyl-phenyl)-ureidomethyl]-benzamide (example 086);  
 4-Cyano-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 103);  
 4-[3-(2,4-Dimethoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 100); and  
 3-Bromo-4-methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 105).

\* \* \* \* \*



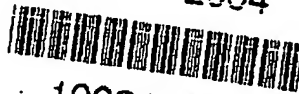
## EXHIBIT B

FORM PTO-1595 (modified)

(Rev. 6-93)

REC'D

01-14-2004



102645416

U.S. DEPARTMENT OF COMMERCE

HEET

Patent and Trademark Office

To the Director of the United States Patent and Trademark Office.

Attached original documents or copies thereof.

## 1. Name of conveying party(ies):

Marco Ciufolini  
Camille Georges Wernuth  
Bruno Marie Gielthen  
Alain Moussy

Additional conveying party(ies) NO

## 2. Name and address of receiving party(ies):

AB Science  
3, Avenue Georges V  
Paris  
75008  
France

2004 JAN 12 AM 8:57  
OPR/FINANCE

## 3. Nature of conveyance:

ASSIGNMENTS

Execution Dates:

10/29/03

Additional name(s) &amp; address(es) attached? NO

## 4. Application number(s) or patent number(s):

If this is being filed together with a new application, the execution date of the application is:

A. Patent Application Number(s):

10/632,101

B. Patent Number(s):

PATENT\_NO

Additional numbers attached? NO

## 5. Name and address of party to whom correspondence concerning document should be mailed:

David P. Lentini  
FOLEY & LARDNER  
One Maritime Plaza  
Sixth Floor  
San Francisco, California 94111-3404

## 6. Total number of applications/patents involved: 1

## 7. Total fee (37 C.F.R. § 3.41): \$40.00

☒ Check Enclosed

Charge to deposit account

## 8. Deposit account number: 19-0741

DO NOT USE THIS SPACE

## 9. Statement and signature:

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document. The Commissioner is hereby authorized to charge any additional recordation fees which may be required in this matter to the above-identified deposit account.

David P. Lentini

1/8/04

Name of person signing

Signature

Date

Total number of pages including cover sheet, attachments, and document: 7

01/13/2004 DBYRNE 00000064 10632101

01 FC:8021

40.00 OP

016.319569.1

PATENT  
REEL: 014872 FRAME: 0028

# ASSIGNMENT

*For good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, each undersigned inventor has sold and assigned, and by these presents hereby sells and assigns, unto*

name and AB SCIENCE  
address of 3, Avenue Georges V  
assignee Paris, France 75008

*(hereinafter ASSIGNEE) all right, title and interest for the United States, its territories and possessions in and to this invention relating to*

*title of invention*

**2-(3-aminoaryl)amino-4-aryl-thiazoles for the treatment of diseases**  
*as set forth in this United States Patent Application*

check one ☐ *executed concurrently herewith*

☐ *executed on*

☒ *Serial No.* 10/632,101 *Filed* AUGUST 1, 2003

*in and to said United States Patent Application including any and all divisions or continuations thereof and in and to any and all Letters Patent of the United States which may issue on any such application or for said invention, including any and all reissues or extensions thereof, to be held and enjoyed by said ASSIGNEE, his successors, legal representatives and assigns to the full end of the term or terms for which any and all such Letters Patent may be granted as fully and entirely as would have been held and enjoyed by the undersigned had this Assignment not been made;*

*Each of the undersigned hereby authorizes and requests the Commissioner of Patents and Trademarks to issue any and all such Letters Patent to said ASSIGNEE, its successors or assigns in accordance herewith;*


*Each of the undersigned warrants and covenants that he has the full and unencumbered right to sell and assign the interests herein sold and assigned and that he has not executed and will not execute any document or instrument in conflict herewith;*

*Each of the undersigned further covenants and agrees he will communicate to said ASSIGNEE, its successors, legal representatives or assigns all information known to him relating to said invention or patent application and that he will execute and deliver any papers, make all rightful oaths, testify in any legal proceedings and perform all other lawful acts deemed necessary or desirable by said ASSIGNEE, its successors, legal representatives or assigns to perfect title to said invention, to said application including divisions and continuations thereof and to any and all Letters Patent which may be granted therefor or thereon, including reissues or extensions, in said ASSIGNEE, its successors, or assigns or to assist said ASSIGNEE, its successors, legal representatives or assigns in obtaining, reissuing or enforcing Letters Patent of the United States for said invention;*

*Each of the undersigned hereby assigns all right title and interest to this invention to said ASSIGNEE for patent applications in any country claiming benefit of the priority of the present United States application.*

## ASSIGNMENT

Each of the undersigned hereby authorizes the firm of **FOLEY & LARDNER** to insert in this Assignment any further identification which may be necessary or desirable to comply with the rules of the U.S. Patent and Trademark Office for recordation of this Assignment.

NAMES AND SIGNATURES OF INVENTORS		
Name: <b>Marco CIUFOLINI</b>	Signature:	Date:
Name: <b>Camille WERMUTH</b>	Signature:	Date:
Name: <b>Bruno GIELTHEN</b>	Signature:	Date:
Name: <b>Alain MOUSSY</b>	Signature 	Date: 10/29/03
NAMES AND SIGNATURES OF WITNESSES		
Name:	Signature:	Date:
Name:	Signature:	Date:
Name:	Signature:	Date:
Name:	Signature:	Date:

Note: Prima facie evidence of execution may optionally be obtained by execution of this document before a U.S. Consul or before a local officer authorized to administer oaths whose authority is proved by a certificate from a U.S. Consul.

# ASSIGNMENT

For good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, each undersigned inventor has sold and assigned, and by these presents hereby sells and assigns, unto

name and AB SCIENCE  
address of 3, Avenue Georges V  
assignee Paris, France 75008

(hereinafter ASSIGNEE) all right, title and interest for the United States, its territories and possessions in and to this invention relating to

title of invention  
2-(3-aminoaryl)amino-4-aryl-thiazoles for the treatment of diseases  
as set forth in this United States Patent Application

check one ☐ executed concurrently herewith  
☐ executed on \_\_\_\_\_  
☒ Serial No. 10/632,101 Filed AUGUST 1, 2003

in and to said United States Patent Application including any and all divisions or continuations thereof and in and to any and all Letters Patent of the United States which may issue on any such application or for said invention, including any and all reissues or extensions thereof, to be held and enjoyed by said ASSIGNEE, its successors, legal representatives and assigns to the full end of the term or terms for which any and all such Letters Patent may be granted as fully and entirely as would have been held and enjoyed by the undersigned had this Assignment not been made;

Each of the undersigned hereby authorizes and requests the Commissioner of Patents and Trademarks to issue any and all such Letters Patent to said ASSIGNEE, its successors or assigns in accordance herewith;

Each of the undersigned warrants and covenants that he has the full and unencumbered right to sell and assign the interests herein sold and assigned and that he has not executed and will not execute any document or instrument in conflict herewith;

Each of the undersigned further covenants and agrees he will communicate to said ASSIGNEE, its successors, legal representatives or assigns all information known to him relating to said invention or patent application and that he will execute and deliver any papers, make all rightful oaths, testify in any legal proceedings and perform all other lawful acts deemed necessary or desirable by said ASSIGNEE, its successors, legal representatives or assigns to perfect title to said invention, in said application including divisions and continuations thereof and to any and all Letters Patent which may be granted therefor or thereon, including reissues or extensions, in said ASSIGNEE, its successors, or assigns or to assist said ASSIGNEE, its successors, legal representatives or assigns in obtaining, reissuing or enforcing Letters Patent of the United States for said invention;

Each of the undersigned hereby assigns all right title and interest to this invention to said ASSIGNEE for patent applications in any country claiming benefit of the priority of the present United States application.

# ASSIGNMENT

Each of the undersigned hereby authorizes the firm of **FOLEY & LARDNER** to insert in this Assignment any further identification which may be necessary or desirable to comply with the rules of the U.S. Patent and Trademark Office for recordation of this Assignment.

NAMES AND SIGNATURES OF INVENTORS		
Name: Marco CIUFOLINI	Signature:	Date:
Name: Camille WERMUTH	Signature: C.G.W. - <i>[Signature]</i>	Date: 10/29/03
Name: Bruno GIELTHEN	Signature: <i>[Signature]</i>	Date: 10/29/03
Name: Alain MOUSSY	Signature:	Date:
NAMES AND SIGNATURES OF WITNESSES		
Name:	Signature:	Date:
Name:	Signature:	Date:
Name:	Signature:	Date:
Name:	Signature:	Date:

Note: Prima facie evidence of execution may optionally be obtained by execution of this document before a U.S. Consul or before a local officer authorized to administer oaths whose authority is proved by a certificate from a U.S. Consul.

# ASSIGNMENT

For good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, each undersigned inventor has sold and assigned, and by these presents hereby sells and assigns, unto

name and AB SCIENCE  
address of 3, Avenue Georges V  
assignee Paris, France 75008

(hereinafter ASSIGNEE) all right, title and interest for the United States, its territories and possessions in and to this invention relating to

title of invention  
2-(3-aminoaryl)amino-4-aryl-thiazoles for the treatment of diseases  
as set forth in this United States Patent Application

check one ☐ executed concurrently herewith  
☐ executed on \_\_\_\_\_  
☒ Serial No. 10/632,101 Filed AUGUST 1, 2003

in and to said United States Patent Application including any and all divisions or continuations thereof and in and to any and all Letters Patent of the United States which may issue on any such application or for said invention, including any and all reissues or extensions thereof, to be held and enjoyed by said ASSIGNEE, its successors, legal representatives and assigns to the full end of the term or terms for which any and all such Letters Patent may be granted as fully and entirely as would have been held and enjoyed by the undersigned had this Assignment not been made;

Each of the undersigned hereby authorizes and requests the Commissioner of Patents and Trademarks to issue any and all such Letters Patent to said ASSIGNEE, its successors or assigns in accordance herewith;


Each of the undersigned warrants and covenants that he has the full and unencumbered right to sell and assign the interests herein sold and assigned and that he has not executed and will not execute any document or instrument in conflict herewith;

Each of the undersigned further covenants and agrees he will communicate to said ASSIGNEE, its successors, legal representatives or assigns all information known to him relating to said invention or patent application and that he will execute and deliver any papers, make all rightful oaths, testify in any legal proceedings and perform all other lawful acts deemed necessary or desirable by said ASSIGNEE, its successors, legal representatives or assigns to perfect title to said invention, to said application including divisions and continuations thereof and to any and all Letters Patent which may be granted therefor or thereon, including reissues or extensions, in said ASSIGNEE, its successors, or assigns or to assist said ASSIGNEE, its successors, legal representatives or assigns in obtaining, reissuing or enforcing Letters Patent of the United States for said invention;

Each of the undersigned hereby assigns all right title and interest to this invention to said ASSIGNEE for patent applications in any country claiming benefit of the priority of the present United States application.

# ASSIGNMENT

Each of the undersigned hereby authorizes the firm of **FOLEY & LARDNER** to insert in this Assignment any further identification which may be necessary or desirable to comply with the rules of the U.S. Patent and Trademark Office for recordation of this Assignment.

NAMES AND SIGNATURES OF INVENTORS		
Name: Marco CIUFOLINI	Signature: 	Date: 10/29/2003
Name: Camille WERMUTH	Signature:	Date:
Name: Bruno GIELTHEN	Signature:	Date:
Name: Alain MOUSSY	Signature:	Date:
NAMES AND SIGNATURES OF WITNESSES		
Name:	Signature:	Date:
Name:	Signature:	Date:
Name:	Signature:	Date:
Name:	Signature:	Date:

Note: Prima facie evidence of execution may optionally be obtained by execution of this document before a U.S. Consul or before a local officer authorized to administer oaths whose authority is proved by a certificate from a U.S. Consul.



## EXHIBIT C

**KINAVET-CA1**  
(masitinib mesylate)  
Tablet  
Antineoplastic

For oral use in dogs only

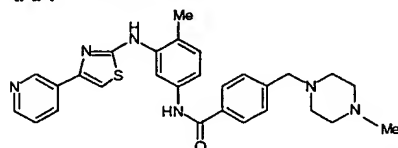
Conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-308.

**CAUTION:**

Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Use only as directed. It is a violation of Federal law to use this product other than as directed in the labeling.

**DESCRIPTION:**

Masitinib is a tyrosine kinase inhibitor. The molecular weight of masitinib base is 498.67. The empirical formula is  $C_{22}H_{20}N_4O_2S$ . The structural formula is:



KINAVET-CA1 tablets are round, biconvex, orange, coated tablets, containing either 50 mg or 150 mg masitinib base as masitinib mesylate. Each tablet is engraved with logo on one side and dosage strength on the other side.

**INDICATIONS:**

KINAVET-CA1 tablets are indicated for the treatment of recurrent (post-surgery) or nonresectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and/or chemotherapy except corticosteroids.

**DOSAGE AND ADMINISTRATION:**

Always provide Client Information Sheet with prescription.

Administer KINAVET-CA1 at an initial dose of 12.5 mg/kg/day (5.7 mg/lb/day) orally, once daily with food (see Table 1). Dose reductions to 9 mg/kg/day (4.1 mg/lb/day, see Table 2) and dose interruptions may be utilized, if needed, to manage adverse reactions (see Table 3 as well as WARNINGS and PRECAUTIONS). Do not split or crush tablets.

Table 1. Initial Dose, 12.5 mg/kg/day Dose Chart

Dog Body Weight		Dose	Number of Tablets	
Pounds	Kilograms		50 mg	150 mg
15.4 - 22.9	7.0 - 10.4	100 mg	2	
23.0 - 30.6	10.5 - 13.9	150 mg		1
30.7 - 39.4	14.0 - 17.9	200 mg	1	1
39.5 - 48.2	18.0 - 21.9	250 mg	2	1
48.3 - 57.0	22.0 - 25.9	300 mg		2
57.1 - 65.8	26.0 - 29.9	350 mg	1	2
65.9 - 74.6	30.0 - 33.9	400 mg	2	2
74.7 - 83.4	34.0 - 37.9	450 mg		3
83.5 - 92.2	38.0 - 41.9	500 mg	1	3
92.3 - 101.0	42.0 - 45.9	550 mg	2	3
101.1 - 110.2	46.0 - 49.9	600 mg		4
110.3 - 118.6	50.0 - 53.9	650 mg	1	4
118.7 - 127.4	54.0 - 57.9	700 mg	2	4
127.5 - 136.2	58.0 - 61.9	750 mg		5
136.3 - 145.0	62.0 - 65.9	800 mg	1	5
145.1 - 153.8	66.0 - 69.9	850 mg	2	5
153.9 - 162.6	70.0 - 73.9	900 mg		6
162.7 - 171.4	74.0 - 77.9	950 mg	1	6
171.5 - 220	78.0 - 100.0	1000 mg	2	6

\*KINAVET-CA1 cannot be safely dosed at the target dose of 12.5 mg/kg in dogs weighing less than 7.0 kg (15.4 lbs)

Table 2. Reduced Dose, 9 mg/kg/day Dose Chart

Dog Body Weight		Dose	Number of Tablets	
Pounds	Kilograms		50 mg	150 mg
15.4 - 22.9	7.0 - 10.4	Discontinue treatment*		
23.0 - 31.7	10.5 - 14.4	100 mg	2	
31.8 - 42.7	14.5 - 19.4	150 mg		1
42.8 - 54.8	19.5 - 24.9	200 mg	1	1
54.9 - 67.1	25.0 - 30.5	250 mg	2	1
67.2 - 79.4	30.6 - 36.1	300 mg		2
79.5 - 91.5	36.2 - 41.6	350 mg	1	2
91.6 - 103.8	41.7 - 47.2	400 mg	2	2
103.9 - 115.9	47.3 - 52.7	450 mg		3
116.0 - 128.3	52.8 - 58.3	500 mg	1	3
128.4 - 140.4	58.4 - 63.8	550 mg	2	3
140.5 - 152.7	64.0 - 69.4	600 mg		4
152.8 - 164.8	69.5 - 74.9	650 mg	1	4
164.9 - 177.1	75.0 - 80.5	700 mg	2	4
177.1 - 220	80.6 - 100.0	750 mg		5

\*KINAVET-CA1 cannot be effectively dosed at 9 mg/kg in dogs weighing less than 10.5 kg (23.0 lbs)

Table 3. Managing Adverse Reactions with Dose Interruption or Reduction

Toxicity	Dose Adjustment
<b>Renal Toxicities and Protein Loss Syndrome</b>	
Hypoalbuminemia (serum albumin < 0.75X ULN) <sup>a</sup> Proteinuria (UPC > 1) Azotemia (BUN or Creatinine > 1.5X ULN <sup>a</sup> )	If the current dose is 12.5 mg/kg, discontinue treatment until resolution, then resume treatment at 9 mg/kg. If the current dose is 9 mg/kg then permanently discontinue treatment.
<b>Non-Regenerative Anemia and Hemolytic Anemia.</b>	
Hematocrit < 30% Hemoglobin < 10 g/dL	Permanently discontinue treatment.
<b>Neutropenia</b>	
Neutrophils < 1500/ $\mu$ L	If the current dose is 12.5 mg/kg, discontinue treatment until resolution, then resume treatment at 9 mg/kg. If the current dose is 9 mg/kg, permanently discontinue treatment.
<b>Hepatic Toxicity</b>	
ALT or AST > 3X ULN Bilirubin > 1.5X ULN	If the current dose is 12.5 mg/kg, discontinue treatment until resolution, then resume treatment at 9 mg/kg. If the current dose is 9 mg/kg, permanently discontinue treatment.
<b>Gastrointestinal Toxicity</b>	
Vomiting and Diarrhea Grade 3 or greater <sup>c</sup>	If the current dose is 12.5 mg/kg, discontinue treatment until resolution, then resume treatment at 9 mg/kg. If the current dose is 9 mg/kg, permanently discontinue treatment.
<b>Other Adverse Reactions</b>	
Severe Weight Loss	Permanently discontinue treatment.

<sup>a</sup>ULN = lower limit of normal

<sup>b</sup>ULN = upper limit of normal

<sup>c</sup>Grade 3 diarrhea is an increase of > 6 stools per day over baseline. Grade 3 vomiting is > 5 vomiting episodes in 24 hours, or vomiting for > 4 days.<sup>1</sup>

**CONTRAINDICATIONS:**

Do not initiate KINAVET-CA1 tablet treatment in dogs with:

- Hypoalbuminemia (serum albumin < 1X ULN)
- Proteinuria (urine protein to creatinine [UPC] ratio > 1)
- Azotemia (elevated blood urea nitrogen or creatinine > 1 ULN)
- Anemia (hematocrit < 30 % or hemoglobin < 10 g/dL)
- Neutropenia (< 2000/ $\mu$ L)
- AST or ALT elevations (> 3X ULN)
- Hyperbilirubinemia (> 1.5X ULN)

Do not use in dogs that are pregnant, lactating, or intended for breeding. Masitinib caused impaired fertility, fetal resorptions and abnormal development (delayed ossification) in rats.

Do not use in dogs that have a hypersensitivity to masitinib.

**WARNINGS:**

Masitinib was associated with life-threatening or fatal hypoalbuminemia and anemia in field studies and the 39-week safety study. The studies provide evidence that severe adverse reactions may be prevented if dogs are monitored for hypoalbuminemia every 2 weeks and for anemia every 4 weeks, and treatment is discontinued if hypoalbuminemia, proteinuria or anemia occur (see Table 3 and ANIMAL SAFETY).

**HUMAN WARNINGS:**

NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN. Children should not come into contact with KINAVET-CA1. Keep children away from feces, urine, or vomit of treated dogs.

To avoid exposure to drug, wash hands with soap and water after administering KINAVET-CA1 and wear protective gloves to prevent contact with feces, urine, vomit, and broken or crushed KINAVET-CA1 tablets. Place all waste material in a plastic bag and seal before general disposal. If eyes are accidentally exposed to the drug, rinse eyes with water immediately. In case of accidental ingestion by a person, seek medical advice immediately, show the package insert or label to the physician.

Pregnant women, women who may become pregnant, or nursing mothers should pay special attention to these handling precautions (see handling instructions above). KINAVET-CA1 may harm an unborn baby (cause birth defects). For pregnant and nursing women, accidental ingestion of KINAVET-CA1 may have adverse effects on pregnancy or the nursing baby.

## PRECAUTIONS:

Dogs on KINAVET-CA1 tablets should be monitored as follows:

**Every 2 weeks:** Hypoalbuminemia  
Proteinuria

**Every 4 weeks:** Azotemia  
Anemia  
Neutropenia  
Elevated AST or ALT  
Hyperbilirubinemia

In case of a positive semi-quantitative test for proteinuria (dipstick protein  $\geq 30$  mg/dL) or clinical signs of anemia or hemolysis, urine protein should be confirmed with a quantitative test (UPC ratio) and the dog should be tested for hypoalbuminemia, anemia, and azotemia.

Refer to Table 3 under DOSAGE AND ADMINISTRATION for management of adverse reactions.

The safe use of KINAVET-CA1 tablets has not been evaluated in dogs younger than 2 years of age. KINAVET-CA1 cannot be safely dosed in dogs weighing less than 7 kg (15.4 lbs).

KINAVET-CA1 is metabolized in the liver. The influence of concomitant drugs that may inhibit metabolism of KINAVET-CA1 tablets has not been evaluated in dogs. Drug compatibility should be assessed for dogs requiring concomitant therapy. Concomitant treatment with drugs which are metabolized by CYP450 isoenzymes (3A4, 3A5, 2C9, 2D6) may result in higher or lower plasma levels of either KINAVET-CA1 or those drugs, and should be used with caution (see CLINICAL PHARMACOLOGY).

The concomitant use of potentially nephrotoxic drugs and KINAVET-CA1 has not been evaluated.

Vascular homeostasis in dogs taking KINAVET-CA1 that require surgery has not been evaluated.

## ADVERSE REACTIONS:

Adverse reactions associated with KINAVET-CA1 treatment include:

<b>General:</b>	lethargy, weakness, dehydration, behavioral changes, death
<b>Gastrointestinal:</b>	vomiting, diarrhea, bloody stools, melena, constipation, decreased appetite, anorexia
<b>Renal:</b>	azotemia, proteinuria, elevated UPC, polyuria, polydipsia, hemoglobinuria, hematuria, nephrotic/protein loss syndrome
<b>Hepatic:</b>	elevated liver enzymes, elevated bilirubin, ascites, icterus
<b>Cardiorespiratory:</b>	cough, pleural effusion, possible pulmonary thromboembolism, dyspnea, hypertension, tachycardia, cardiomegaly, syncope, circulatory collapse, aspiration pneumonia
<b>Metabolic:</b>	pancreatitis, weight loss, tumor lysis syndrome, mast cell degranulation, periodic hypoglycemia
<b>Hematologic:</b>	anemia, hemolytic anemia, non-regenerative anemia, leukopenia, neutropenia, lymphopenia, thrombocytopenia
<b>Ocular:</b>	hyphema
<b>Skin:</b>	alopecia, increased incidence of lipomas, subcutaneous edema, pruritis
<b>Other:</b>	lymphadenopathy, hemoabdomen, back pain

Refer to Table 3, under DOSAGE AND ADMINISTRATION for management of adverse reactions.

For a copy of the Material Safety Data Sheet (MSDS) or to report adverse reactions, contact .AB Science, USA at 973-218-2436 or contact@ab-science.com.

## INFORMATION FOR DOG OWNER:

The dog owner or person responsible for administering KINAVET-CA1 to the dog should receive and read the Client Information Sheet, which describes how to safely administer KINAVET-CA1, monitor for possible adverse reactions and clean up any urine, feces or vomit from dogs treated with KINAVET-CA1. The Client Information Sheet also contains warnings for humans and what to do in case of accidental human exposure to KINAVET-CA1.

## CLINICAL PHARMACOLOGY:

Masitinib is a protein-tyrosine kinase inhibitor. Protein tyrosine kinases are thought to be activated in cancer cells and to drive tumor progression. Tyrosine kinase inhibitor drugs act by interfering with these cell communications and may prevent tumor growth. *In vitro*, masitinib selectively inhibits the mutated form of the c-Kit receptor (a receptor tyrosine kinase) in the juxtamembrane region and the c-Kit wild-type receptor. It also inhibits the platelet-derived growth factor receptor and the fibroblast growth factor receptor 3.

Following oral administration of  $11.2 \pm 0.5$  mg/kg masitinib, as KINAVET-CA1 tablets, in dogs, masitinib was rapidly absorbed reaching a mean ( $\pm$  1SD) peak plasma concentration of  $895 (\pm 283)$  ng/mL at  $2.29 (\pm 0.83)$  hours. The mean area under the plasma concentration time-curve (AUC 0-24) was  $5.70 (\pm 1.93)$   $\mu\text{g} \times \text{hr/mL}$ . The mean elimination half-life ( $t_{1/2}$ ) is  $3.24 (\pm 0.42)$  hours. Following administration of KINAVET-CA1 tablets, the fed  $C_{\text{max}}$  was 136% (90% Confidence Limits: 98 – 190%) and the fed AUC was 114% (52 – 252%) of the fasted  $C_{\text{max}}$  and AUC, respectively.

The plasma total body clearance and volume of distribution of masitinib in normal healthy Beagle dogs is approximately 14 mL/min/kg and 17 L/kg, respectively. Masitinib is approximately 90% bound to plasma proteins. Minimal accumulation occurs when masitinib is administered daily at a dose of 12.5 mg/kg. Based on masitinib plasma concentrations at clinically relevant doses in toxicity studies, the inter-animal coefficient of variation in AUC (representing bioavailability) is expected to be about 25%.

Masitinib is metabolized predominantly by N-dealkylation. Elimination is principally in the bile and gastrointestinal tract. *In vitro* testing with human liver microsomes demonstrated that masitinib inhibits the activity of cytochrome P450 isozymes CYP2C9, 2D6, 3A4 and 3A5. Results of *in vitro* testing with human hepatocytes were inconsistent; therefore, the potential for masitinib to induce the activity of cytochrome P450 isozymes is unclear.

## EFFECTIVENESS:

### Reasonable Expectation of Effectiveness

Effectiveness has not been demonstrated for KINAVET-CA1. A reasonable expectation of effectiveness for conditional approval was based on time to progression (TTP) in a subpopulation of dogs in the following study.

A randomized, placebo controlled, double masked, multi-center field study was conducted to evaluate the safety and effectiveness of KINAVET-CA1 in dogs with Grade II or III cutaneous mast cell tumors recurrent after surgery or nonresectable without regional lymph node involvement. Two hundred and two dogs of various breeds, were enrolled. 161 received KINAVET-CA1 at a starting dose of 12.5 mg/kg orally and 41 received placebo, daily for 6 months, or until disease progression or withdrawal from the study for another cause.

The primary variable, objective response rate after 4 months of treatment, confirmed after 6 months of treatment, failed to show a statistically significant difference between the KINAVET-CA1 and placebo treated dogs: 16.1% of dogs administered KINAVET-CA1 had a complete or partial response compared to 14.6% of dogs administered placebo.

The primary variable failed. However, one of the secondary variables, TTP, in a subpopulation of dogs that did not receive previous chemotherapy and/or radiotherapy except corticosteroids, demonstrated a reasonable expectation of effectiveness. One hundred and thirteen dogs treated with KINAVET-CA1 had an increase in median TTP of 52.5 days compared to 30 dogs treated with placebo ( $p$ -value=0.0143). The median TTP in the KINAVET-CA1 group was 118 days, 80% longer than the placebo group with a median time to progression of 65.5 days. The study was not designed for TTP to support substantial evidence of effectiveness.

## ANIMAL SAFETY:

The margin of safety and toxicity profile of masitinib (not commercial formulation) was evaluated in three laboratory safety studies (for 4, 13, and 39 weeks) in healthy 6 to 7 month old Beagle dogs. Masitinib has a narrow margin of safety, and one death occurred after 33 weeks of treatment with 20.9 mg/kg/day, a dose comparable to 1.4X the maximum KINAVET-CA1 label dose of 15.0 mg/kg/day. (See Safety Study Results, below. See Table 3, WARNINGS and PRECAUTIONS for risk management.) The results of the safety studies provide the following toxicity profile for masitinib: bone marrow suppression (anemia, neutropenia, and bone marrow hypocellularity), evidence of red blood cell sequestration (splenic hemosiderosis), proteinuria and hypoalbuminemia without kidney lesions on histopathology, liver abnormalities (mildly increased liver enzymes, histopathologic lesions), gastrointestinal signs, and increased coagulation values. The 13-week safety study provides evidence that these adverse effects are reversible.

**Safety Studies Results:** There were no signs of toxicity at 2.1 mg/kg (0.14X) for 39 weeks or 3.5 mg/kg (0.23X) for 13 weeks.

In the 4, 13, and 39-week studies at 7.0 mg/kg (0.5X) and 10.5 mg/kg (0.7X), clinical signs included transient and infrequent vomiting, soft feces, lethargy, and muscle weakness; erythema of the neck or muzzle, pallor, mild anemia, and mild proteinuria. After 39 weeks at 7.0 mg/kg (0.5X), histopathology findings included splenic hemosiderosis, brownish pigment deposits in hepatic Kupfer cells and lymph nodes, and increased lipid tissue in the bone marrow.

In the 39-week study at 20.9 mg/kg (1.4X), a female developed severe hypoalbuminemia and proteinuria, and moderate anemia, by week 25. She was euthanized in week 33 because of ascites, emaciated appearance, decreased appetite, lateral recumbency, pallor, and severe anemia, hypoalbuminemia, hypoproteinemia, and proteinuria. She had thrombocytosis, hematuria, lymphopenia, and increased activated partial thromboplastin time (APTT), fibrinogen, and blood urea nitrogen. Necropsy and histopathology findings included pericardial, subcutaneous, and tissue edema, and severe lymphoid depletion of the thymus. Other dogs on 20.9 mg/kg (1.4X) masitinib had vomiting, lethargy, pallor, erythema of the neck, hind leg stiffness, mild anemia, neutropenia, hypoalbuminemia, and proteinuria. Histopathology findings were similar to those at 7.0 mg/kg (0.5X), but more pronounced.

In the 4 and 13-week studies at 35.1 mg/kg (2.3X), clinical signs included vomiting, diarrhea, pallor, and lethargy. Clinical pathology findings included anemia, neutropenia, decreased eosinophils, and mild hypoalbuminemia, and mild increases in APTT, fibrinogen, and liver enzymes (alanine aminotransferase and alkaline phosphatase). Histopathology findings included slight hepatocellular hypertrophy, bile canaliculi plugs, vacuolated and brownish pigment-laden Kupfer cells in the liver, cystic epithelial hyperplasia of the gall bladder, foamy macrophages in the mesenteric lymph node, chronic interstitial pneumonitis, acute esophagitis, increased lipid tissue in the bone marrow, and bone marrow hypocellularity.

After 13 weeks of treatment, a subset of dogs from the 35.1 mg/kg (2.3X) treatment group were given a 4-week treatment-free recovery period. At the end of this period, the recovery dogs did not have the adverse clinical pathology and histopathology findings that were observed in dogs at the end of the 13 weeks of treatment.

In the 4-week study at 105.5 mg/kg (7.0X), clinical signs, clinical pathology, and histopathology results were similar but more severe than at 35.1 mg/kg (2.3X), and also included blood-tinged feces, decreased appetite, increased heart rate, weight loss, proteinuria, hematuria, hepatomegaly, vacuolated hepatocytes, a markedly increased myeloid to erythroid ratio, lymphoid depletion of the thymus, histiocytosis in the spleen, and foamy alveolar macrophages in the lungs.

## STORAGE CONDITIONS:

Keep at controlled room temperature (15-25°C; 59-77°F), in the original packaging, away from a source of heat or humidity.

## HOW SUPPLIED:

KINAVET-CA1 is supplied in white high density polyethylene (HDPE) bottles containing 30 tablets of 50mg masitinib base or 150mg masitinib base.

## REFERENCES:

1. Veterinary co-operative oncology group – common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy in dogs and cats v1.0. *Vet Comp Oncol* 2004;2(4):195-213.

Manufactured by:  
Catalent Pharma Solutions  
Somerset, NJ 08873  
USA

Manufactured for:  
AB Science  
3, Avenue George V  
75003 – PARIS (France)

Client	AB Science
Contact	Cyrille Denariez


ALIAS

Dossier	
Produit	7531
Réf	Kinavel™ CA1
	V01
Dimensions	210x297 mm
	19/11/2010

BAT : date et signature

Client	AB Science
Contact	Cyrille Denariez

Dossier	7535
Produit	Kinavet™ CA1
Réf	Etui 150 mg - US - V1
	1 langue
Dimensions	45 x 45 x 85 mm
	19/11/2010

 <p><b>KINAVET-CA1</b> masitinib mesylate Tablet Antineoplastic <b>150 mg</b> 30 coated tablets</p> <p>Conditionally approved by FDA pending a full demonstration of effective- ness under application number 141-308</p>	<p><b>KINAVET-CA1 150 mg</b></p> <p>For oral use in dogs only</p> <p><b>INDICATION</b> For the treatment of recurrent (post surgery) or non resectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and / or chemotherapy except corticosteroids.</p> <p><b>CAUTION</b> Federal law restricts this drug to use by or on order of a licensed veterinarian. Use only as directed. It is a violation of Federal law to use this product other than as directed in the labeling.</p> <p>See enclosed package insert for dosing information and important human safety information. Wear gloves when handling this drug.</p> <p>Manufactured by: Catalent Pharma Solutions 14 Schoolhouse Road Somerset NJ 08873 USA For: AB Science 3 avenue George V F-75008 Paris</p>	<p><b>HUMAN WARNINGS</b> NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN. Children should not come into contact with KINAVET-CA1. Keep children away from feces, urine and vomit of treated dogs. To avoid exposure to drug, wash hands with soap and water after administering KINAVET-CA1 and wear protective gloves to prevent contact with feces urine, vomit, and broken or crushed KINAVET-CA1 tablets. Place all waste material in plastic bag and seal before general disposal. If eyes are accidentally exposed to the drug, rinse eyes with water immediately. In case of accidental ingestion by a person, seek medical advice immediately, show the package insert or label to the physician. Pregnant women, women who may become pregnant, or nursing mothers should pay special attention to these handling precautions as KINAVET-CA1 belongs to a class of agents that may cause harm to the unborn baby. Keep at controlled room temperature below 25°C (&lt;77°F) in the original packaging away from a source of heat or humidity.</p>	<p>Lot: EXP:</p> <p><b>CONTRAINDICATIONS:</b> Do not initiate KINAVET-CA1 tablets treatment in dogs with proteinuria (a urine protein to creatinine (UPC) ratio &gt; 1), hypoalbuminemia (serum albumin &lt;1 time the lower limit of normal (1xULN)), elevated blood urea nitrogen or creatinine (&gt;1 time the upper normal limit (1xULN)), anemia (hematocrit &lt;30% or hemoglobin &lt;10g/dl), neutropenia (&lt;2000 mm<sup>3</sup>), hyperbilirubinemia (&gt;1.5 times the upper normal limit (1.5xULN), or ASAT/ALT &gt;3 times the upper limit of normal (3xULN)).</p> <p>Do not use in dogs that are pregnant, lactating or intended for breeding. KINAVET-CA1 caused impaired fertility, fetal resorptions and abnormal development (delayed ossification) in rats.</p> <p>Do not use in dogs that have demonstrated hypersensitivity to masitinib.</p>
<p><b>7535 - V1</b></p> <p><i>ALIAS</i></p> <p><b>BAT : date et signature</b></p>			

AB Science, 3 avenue George V, F-75008 Paris



**150 mg**  
Antineoplastic  
Tablet  
**KINAVET-CA1**  
masitinib mesylate



7535 - V1

Client	AB Science
Contact	Cyrille Denarez

Dossier	7533
Produit	Kinavet™ CA
Réf	Etiquette 150 mg 1 langue - US - V1
Dimensions	110 x 45 mm
	19/11/2010

*ALIAS*

BAT : date et signature	
-------------------------	--

7533 -  
For oral use in dogs only.

CAUTION: Federal law restricts this drug to use by or on order of a licensed veterinarian. Use only as directed. It is a violation of Federal law to use this product other than as directed in the labeling.

See enclosed package insert for dosing information and important human safety information. Wear gloves when handling this drug.

Manufactured by: Catalent Pharma Solutions  
14 Schoonhouse Road Somerset NJ 08873 USA  
For AB Science 3 Avenue George IV-15008 Paris



**KINAVET-CA1**  
masitinib mesylate  
Tablet  
Antineoplastic  
**150 mg**

30 coated tablets

Conditionally approved by FDA  
pending a full demonstration of  
effectiveness under application  
number 141-308

HUMAN WARNINGS:  
NOT FOR USE IN HUMANS. KEEP THIS  
AND ALL MEDICATION OUT OF THE REACH  
OF CHILDREN.

Keep at controlled room temperature below  
25°C (<77°F) in the original packaging away  
from a source of heat or humidity.

Lot:

EXP:

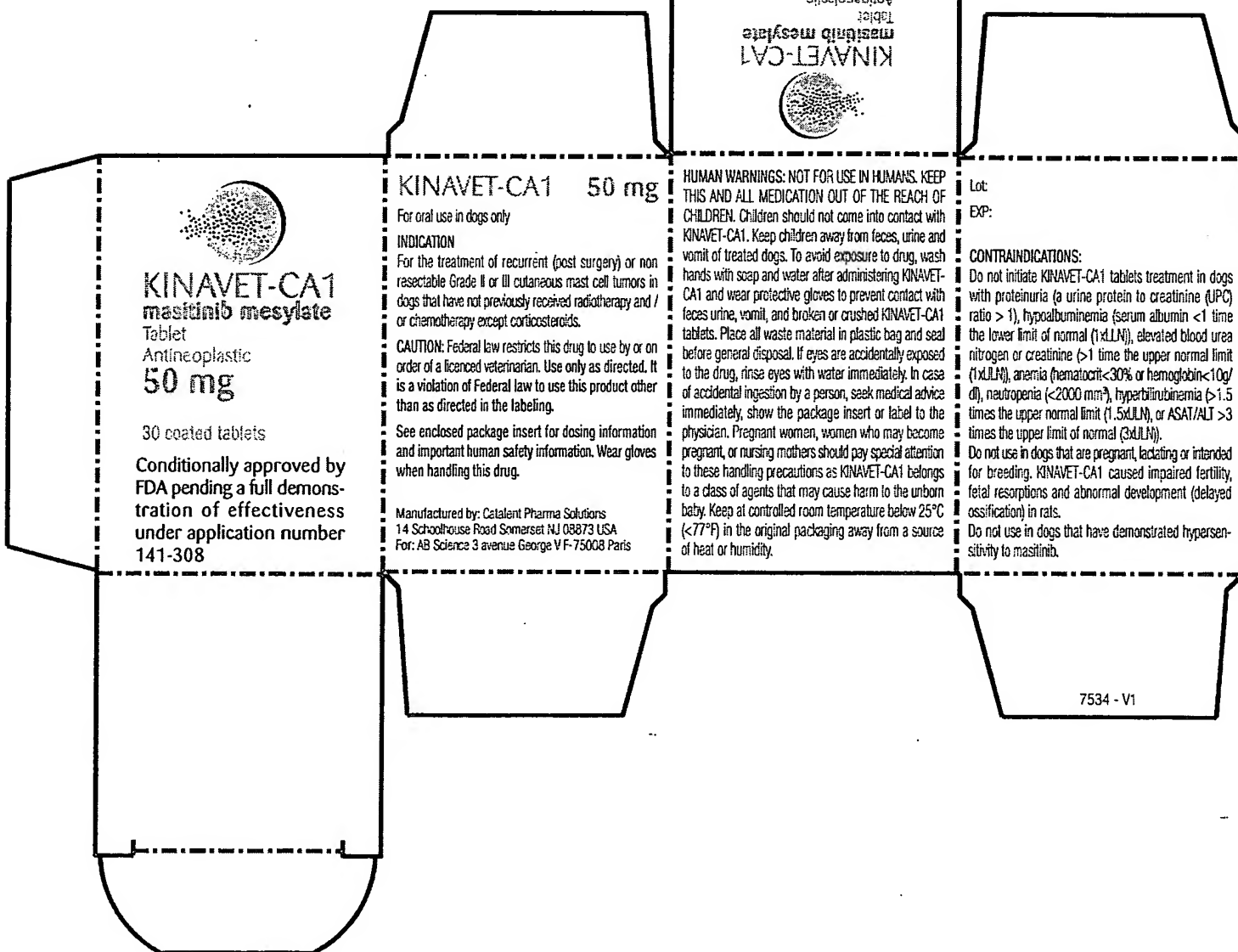
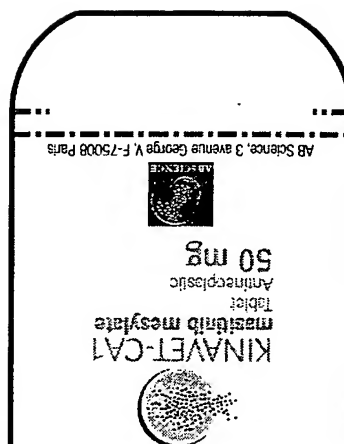
www.kinavet.com

Client	AB Science
Contact	Cyrille Denariez

Dossier	7534
Produit	Kinavet™ CA1
Réf	Etui 50 mg - US - V1
	1 langue
Dimensions	45 x 45 x 65 mm
	19/11/2010

ALIAS

BAT : date et signature



## KINAVET-CA1 50 mg

For oral use in dogs only

### INDICATION

For the treatment of recurrent (post surgery) or non resectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and / or chemotherapy except corticosteroids.

**CAUTION:** Federal law restricts this drug to use by or on order of a licensed veterinarian. Use only as directed. It is a violation of Federal law to use this product other than as directed in the labeling.

See enclosed package insert for dosing information and important human safety information. Wear gloves when handling this drug.

Manufactured by: Catalent Pharma Solutions  
14 Schoolhouse Road Somerset NJ 08873 USA  
For: AB Science 3 avenue George V F-75008 Paris

**HUMAN WARNINGS:** NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN. Children should not come into contact with KINAVET-CA1. Keep children away from feces, urine and vomit of treated dogs. To avoid exposure to drug, wash hands with soap and water after administering KINAVET-CA1 and wear protective gloves to prevent contact with feces, urine, vomit, and broken or crushed KINAVET-CA1 tablets. Place all waste material in plastic bag and seal before general disposal. If eyes are accidentally exposed to the drug, rinse eyes with water immediately. In case of accidental ingestion by a person, seek medical advice immediately, show the package insert or label to the physician. Pregnant women, women who may become pregnant, or nursing mothers should pay special attention to these handling precautions as KINAVET-CA1 belongs to a class of agents that may cause harm to the unborn baby. Keep at controlled room temperature below 25°C (<77°F) in the original packaging away from a source of heat or humidity.

Lot:  
EXP:

### CONTRAINDICATIONS:

Do not initiate KINAVET-CA1 tablets treatment in dogs with proteinuria (a urine protein to creatinine (UPC) ratio > 1), hypoalbuminemia (serum albumin <1 time the lower limit of normal (1xULN)), elevated blood urea nitrogen or creatinine (>1 time the upper normal limit (1xULN)), anemia (hematocrit <30% or hemoglobin <10g/dl), neutropenia (<2000 mm<sup>3</sup>), hyperbilirubinemia (>1.5 times the upper normal limit (1.5xULN), or ASAT/ALT >3 times the upper limit of normal (3xULN)).

Do not use in dogs that are pregnant, lactating or intended for breeding. KINAVET-CA1 caused impaired fertility, fetal resorptions and abnormal development (delayed ossification) in rats.

Do not use in dogs that have demonstrated hypersensitivity to mastinib.

7534 - V1

Client	AB Science
Contact	Cyrille Denariez

Dossier	7532
Produit	Kinavet™ CA1
Réf	Etiquette 50 mg 1 langue US - V1
Dimensions	110 x 28 mm
	19/11/2010

ALIAS

BAT : date et signature

30 coated tablets. For oral use in dogs only.  
CAUTION: Federal law restricts this drug to use by or on order of a licensed veterinarian. Use only as directed. It is a violation of Federal law to use this product other than as directed in the labeling. See enclosed package insert for dosing information and important human safety information. Wear gloves when handling this drug.

Manufactured by Calvert Pharma Solutions  
14250 Highway Road, Columbia, NJ 08027 USA  
P.O. Box 1000, 10000 Highway 100, 10000 USA



**KINAVET-CA1**  
moxidectin mesylate

Tablet  
Antiparasitaire

50 mg

Conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-308

HUMAN WARNINGS: NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN. Keep at controlled room temperature below 25°C (77°F) in the original packaging away from a source of heat or humidity.

Lot:

EXP:

www.kinavet.com



## EXHIBIT D

**Application No. 141-308-A-0000-OT**  
**CONDITIONAL APPROVAL DATE: December 15, 2010**  
**CVM#201083**



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR VETERINARY MEDICINE**

**FACSIMILE TRANSMISSION**

<b>DATE:</b> December 15, 2010	<b>TIME:</b> 4:00 p.m.
<b>TO:</b> The Anson Group Attention: Michael R. Langley DVM, MBA, RAC US Agent on behalf of AB Science 11460 North Meridian Street Carmel, IN 46032	<b>FROM:</b> <input type="checkbox"/> Dr. Mary Allen <input type="checkbox"/> Dr. Mohammad Sharar <input type="checkbox"/> Ms. Bonnie Bodo <input checked="" type="checkbox"/> Dr. Robin Keyser OFFICE OF NEW ANIMAL DRUG EVALUATION HFV-107
<b>TEL:</b> 317-569-9500 Ext.103	<b>DHHS/FDA/CVM/ONADE/HFV-107</b> <b>TEL.</b> <input type="checkbox"/> (240) 276-8128 <input type="checkbox"/> (240) 276-9179 <input type="checkbox"/> (240) 276-8198 <input checked="" type="checkbox"/> (240) 276-8130
<b>FAX:</b> 317-569-9520	<b>METRO PARK NORTH II</b> 7500 STANDISH PLACE ROCKVILLE, MD 20855

Number of pages (including cover sheet): 3

CVM/ONADE FAX NUMBER: (240) 276-8242



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Food and Drug Administration  
Rockville MD 20857

DEC 15 2010

Application Number 141308-A-0000-OT

The Anson Group  
Attention: Michael R. Langley DVM, MBA, RAC  
US Agent on behalf of AB Science  
11460 North Meridian Street  
Carmel, IN 46032

Re: Request for conditional approval of KINAVET-CA1

Dear Dr. Langley:

We conditionally approve your conditional approval application for one year for KINAVET-CA1 dated July 9, 2010, amended July 22, 2010 (M-0001), September 2, 2010 (M-0002), and September 16, 2010 (M-0003), under section 571(b) of the Federal Food, Drug, and Cosmetic Act (the act). KINAVET-CA1 (masitinib mesylate) Tablets is conditionally approved for the treatment of recurrent (post-surgery) or nonresectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and/or chemotherapy except corticosteroids in dogs. We forwarded a notice of this conditional approval for publication in the FEDERAL REGISTER. You must notify us of any change to the conditions established in this conditional approval according to 21 CFR 514.8. In addition, you must comply with the records and reporting requirements concerning post-approval experience with this conditionally approved new animal drug according to 21 CFR 514.80. If you fail to make the required reports or maintain the required records under 21 CFR 514.80, your conditional approval would be subject to the withdrawal provisions of section 571(e)(3) of the act.

This application for conditional approval is conditionally approved for one year from the date of this letter. This application is renewable annually for up to four additional one-year terms. A request to renew this application must be submitted no later than 90 days from the end of the one-year period starting on the date of this letter. This request must include sufficient information to show that you are making sufficient progress toward meeting the approval requirements under section 512(d)(1)(E) of Federal Food, Drug, and Cosmetic Act (the act), that the quantity of the drug distributed is consistent with the conditionally approved intended use and conditions of use, and the same drug in the same dosage form for the same intended use has not received approval under Section 512.

KINAVET-CA1 in the dosage form and the intended uses conditionally approved by FDA under application number 141-308 qualifies for seven years of exclusive marketing rights beginning as of the date of this conditional approval letter. Your new animal drug qualifies

Application Number 141308-A-0000-OT

Page 2

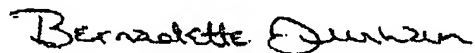
for exclusive marketing rights under section 573(c) of the Federal Food, Drug, and Cosmetic Act (the act) because it has been declared a designated new animal drug by FDA under section 573(a) of the act. Any remaining portion of the exclusive marketing period will apply to a fully approved product if there is no lapse in the conditional approval status and full approval is obtained within five years of this conditional approval.

Your final printed labeling must be identical to the approved facsimile labeling submitted September 16, 2010 (N-141308-M-0003) except change the Caution statement on the package insert, carton and bottle label, from "*Extra-label use of this drug is prohibited by Federal law.*" to "*It is a violation of Federal law to use this product other than as directed in the labeling.*" Please submit in triplicate three paper copies (a total of nine copies) of each component of the final printed labeling before distributing and marketing your new animal drug.

The expiration dating for this new animal drug is 24 months. Under current good manufacturing practice (cGMP) regulations (21 CFR 211 and 226), you are required to validate your manufacturing processes. This validation provides assurance that the manufacturing processes will reliably meet predetermined specifications. This validation is demonstrated by documenting that the manufacturing processes are adequate to preserve the identity, strength, quality, and purity of the new animal drug. If your validation information was not available or was found deficient at the time of the pre-approval inspection, you should contact FDA after you complete manufacturing validation and before you ship the product. A product that does not conform to cGMP is adulterated under section 501(a) of the act.

If you submit correspondence relating to this conditional approval, your correspondence should reference the date and the principal submission identifier found at the top of this letter. If you have any questions or comments, contact Dr. Mary E. Allen, Acting Director, Division of Therapeutic Drugs for Non-Food Animals, at 240-276-8337.

Sincerely,



Bernadette M. Dunham, D.V.M., Ph.D.

Director

Center for Veterinary Medicine

Enclosure:

Freedom of Information Summary

## EXHIBIT E

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING  
REJECTION OVER A PENDING "REFERENCE" APPLICATION**

Docket Number (Optional)  
065691-0332

In re Application of: Marco Ciufolini et al.

Application No.: 10/632,101

Filed: August 1, 2003

For: 2-(3-aminoaryl)amino-4-aryl-thiazoles for the Treatment of Diseases

The owner\*, AB Science, 3 av George V, Paris, France, of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number 11/779,633, filed on July 18, 2007, as such term is defined in 35 U.S.C. 154 and 173, and as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that: any such patent: granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 39,221



Signature

April 10, 2008

Date

Rouget F. Henschel

Typed or printed name

(202) 295-4059

Telephone Number

- ☒ Terminal disclaimer fee under 37 CFR 1.20(d) is included.

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

\*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).

Form PTO/SB/96 may be used for making this statement. See MPEP § 324.

This collection of information is required by 37 CFR 1.321. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

## EXHIBIT G

Date of Approval: DEC 15 2010

# FREEDOM OF INFORMATION SUMMARY

## APPLICATION FOR CONDITIONAL APPROVAL

Application 141-308

KINAVET-CA1

Masitinib mesylate  
Tablet  
Dog

For the treatment of recurrent (post-surgery) or nonresectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and/or chemotherapy except corticosteroids

Sponsored by:

AB Science

Paris, France



## TABLE OF CONTENTS

I. GENERAL INFORMATION:	1
II. EFFECTIVENESS:	2
A. Dosage Characterization:	2
B. Reasonable Expectation of Effectiveness:	3
III. TARGET ANIMAL SAFETY:	5
A. Relative Bioavailability (Bridging) Study	5
B. 4-Week Toxicity Study	7
C. 13-Week Toxicity Study	14
D. 39-Week Toxicity Study	19
IV. HUMAN FOOD SAFETY:	25
V. USER SAFETY:	25
VI. AGENCY CONCLUSIONS:	26
A. Marketing Status:	26
B. Exclusivity:	26
C. Patent Information:	26
VII. ATTACHMENTS:	27

**I. GENERAL INFORMATION:**

**A. Application Number:** 141-308

**B. Sponsor:** AB Science  
3 Avenue George V  
75008 Paris, France

Drug Labeler Code: 052913

US Agent:  
Michael R. Langley, DVM, MBA, RAC  
The Anson Group  
11460 North Meridian Street  
Carmel, Indiana USA 46032

**C. Proprietary Name(s):** KINAVET-CA1

**D. Established Name(s):** Masitinib mesylate

**E. Pharmacological Category:** Anti-neoplastic

**F. Dosage Form(s):** Tablet

**G. Amount of Active Ingredient(s):** 50 mg or 150 mg

**H. How Supplied:** KINAVET-CA1 tablets are available as round biconvex orange coated tablets. Each tablet is engraved with the logo on one side and the mg strength on the other side. The tablets are packaged in 30-count bottles.

**I. How Dispensed:** Rx

**J. Dosage(s):** 12.5 mg/kg/day (5.7 mg/lb/day)

**K. Route(s) of Administration:** Oral

**L. Species/Class(es):** Dog

**M. Indication(s):** For the treatment of recurrent (post-surgery) or nonresectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and/or chemotherapy except corticosteroids.

## II. EFFECTIVENESS:

The active ingredient in KINAVET-CA1 is referred to as masitinib or AB1010 and the two names are used interchangeably.

**Conditional Dose:** The conditional dose for the indication “for the treatment of recurrent (post-surgery) or nonresectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and/or chemotherapy except corticosteroids” is 12.5 mg/kg/day (5.7 mg/lb/day). The safety data and reasonable expectation of effectiveness data presented in this document and the data to demonstrate a reasonable expectation of effectiveness provide support for this conditional use.

### A. Dosage Characterization:

Three toxicity studies were conducted for target animal safety and were used to help identify a conditional dose in dogs. The conditional dose of 12.5 mg/kg/day was chosen based upon the maximum tolerated dose. See TARGET ANIMAL SAFETY for more information.

In the uncontrolled field study AB03099 titled “Efficacy and Safety of AB1010 in the Treatment of Canine Mast Cell Tumors” conducted in 13 dogs with Grade II or III mast cell tumors, 10 dogs received masitinib mesylate at a dose of 12.5 mg/kg once daily, 2 dogs received 15 mg/kg twice daily and 1 dog received 4.4 mg/kg once daily. The study assessed the effectiveness and safety of masitinib mesylate on canine mast cell tumors based on objective response rate (complete and partial response) over a 12-week period. The objective tumor response was defined as the ratio of current tumor volume to baseline tumor volume and expressed as a percentage: tumor response =  $100 \times (\text{current volume} / \text{baseline volume})$ . Complete response was defined as a tumor response equal to 0%. Partial response was defined as a tumor response  $\leq 50\%$ , with no increase in size of a previously documented lesion or development of new lesions. Four dogs were removed from analysis; 1 dog had a Grade I mast cell tumor and 3 were treated for 10 days or less. The analysis showed 2 out of 9 dogs had a complete response and 2 out of 9 had a partial response at 12 weeks. The objective response was 44% (4/9). One dog with complete response received the 4.4 mg/kg once daily dose. The other 3 dogs with objective response received the 12.5 mg/kg once daily dose. Neutropenia and vomiting were the most common adverse reactions. Edema was also seen. Two dogs were euthanized: 1 for vomiting and lethargy, and 1 for gastric ulcerations, vomiting, and increased liver values. Based on the objective response rate achieved, this study contributed to justifying 12.5 mg/kg/day as an effective dose for treatment.

Masitinib systemic bioavailability was slightly greater following co-administration with food. The effect of food on the pharmacokinetics of masitinib mesylate tablets was tested in a laboratory study of 6 male 8 month old Beagle dogs, using a crossover design and a 7-day washout period. For the fasted treatment, dogs were fasted overnight and food was given 4 hours after a dose of 11.9 mg/kg masitinib mesylate tablets. For the fed treatment, dogs were fed half of their daily ration 30 minutes before dosing and the remaining half immediately after a dose of 11.6 mg/kg masitinib mesylate tablets. The

Fed mean area under the plasma masitinib concentration time-curve (AUC) was 114% (90% Confidence Limits: 52 to 252%) of the Fasted AUC. The Fed mean peak plasma masitinib concentration ( $C_{max}$ ) was 136% (90% Confidence Limits: 98-190%) of the Fasted  $C_{max}$ , and occurred earlier. The time to peak plasma masitinib concentration ( $T_{max}$ ) occurred at 1 to 2 hours for fed versus 1 to 4 hours fasted.

**B. Reasonable Expectation of Effectiveness:**

The multi-center field study AB04003 titled "Multicentric, randomized, double-blind, placebo-controlled clinical field study to demonstrate the efficacy and safety of AB1010 in the control/treatment of Mast Cell Tumors in dogs" was evaluated to support a reasonable expectation of effectiveness for conditional approval. Two hundred and two dogs with Grade II or III mast cell tumors recurrent after surgery or nonresectable without regional lymph node or systemic involvement were enrolled. One hundred and sixty-one received KINAVET-CA1 tablets at a starting dose of 12.5 mg/kg/day and 41 received a placebo tablet. The objective was to demonstrate the effectiveness and safety of masitinib mesylate at the dose of 12.5 mg/kg/day in comparison to placebo.

Enrolled dogs had at least 1 tumor that measured a minimum of 10 mm in diameter. Dogs were excluded if they had renal insufficiency, gastrointestinal bleeding, neutropenia, elevated liver transaminases, other serious diseases, been previously treated with a tyrosine kinase inhibitor, were lactating or pregnant, intended for breeding, under 6 months of age, or weighed less than 3.3 kg.

Variables Measured

The primary evaluation of effectiveness was based on the objective response rate (complete response and partial response) after 4 months (Day 112) of treatment and confirmed after 6 months (Day 168) of treatment. See Table 1 below.

Table 1: Disease Response Definitions

Response	Definition
Complete Response (CR)	Tumor response <sup>a</sup> = 0%
Partial Response (PR)	Tumor response $\leq$ 51%, with no increase in size of previously documented area or any new lesion development.
Stable Disease (SD)	Tumor response between 51% to 124% with no increase in size of previously documented area or any new lesion development.
Progressive Disease (PD)	All other cases.

<sup>a</sup> Tumor response =  $100 \times (\text{current volume}/\text{baseline volume})$

Secondary variables evaluated during the study included time to progression (TTP), progression-free survival, overall survival, best response rate, complete response rate at each time point, overall response rate, and control disease rate. In addition, these

variables were analyzed for different sub-populations including dogs not treated previously with chemotherapy and/or radiotherapy except corticosteroids.

The dogs were examined on day 0, 7, 14, 28, 42, 56, 84, 112, 140 and 168. Tumor assessment, complete blood count (CBC), chemistry profile and urinalysis were performed at each visit. Dose interruptions and/or dose reductions to 9 mg/kg could be made at these visits if adverse reactions occurred. Minimum hematological and biochemical values required to continue treatment at 12.5 mg/kg/day or the reduced dose: neutrophil count > 1000/ $\mu$ L, hematocrit > 20%, platelet count > 100,000/ $\mu$ L, liver transaminases  $\leq$  5.0 times the upper limit normal, and creatinine < 4.0 mg/dL.

### Results

The study, designed to measure the primary variable, objective response rate, failed to show a statistically significant difference between the masitinib mesylate and placebo treated dogs. In the intent to treat population, 16.1% of the patients on masitinib mesylate responded to treatment, compared to 14.6% on placebo. When evaluating a subpopulation of no previous chemotherapy and/or radiotherapy except corticosteroids, 18.9% of the patients on masitinib mesylate responded to treatment, compared to 10.0% on placebo. The intent to treat population included all dogs enrolled in the study.

Table 2: Objective Response Rate in the Intent to Treat Population

Objective Tumor Response	Masitinib % Response	Placebo % Response	P-value <sup>a</sup>
All dogs (n = 202)	16.1	14.6	0.831
No previous chemotherapy/ radiotherapy (n = 152)	18.9	10.0	0.294

<sup>a</sup> Exact Cochran-Mantel-Haenszel test comparing treatments, stratified on tumor grade and type

Although the primary variable failed, one of the secondary variables, time to progression, demonstrated significance in the no previous chemotherapy and/or radiotherapy except corticosteroids sub-population. The secondary variable provides the basis for reasonable expectation of effectiveness. This analysis is based on the per protocol population, which only included dogs that met the entrance criteria for the study.

Table 3: Time to Progression in the Per Protocol Population

Time to Progression	Median Masitinib (days)	Median Placebo (days)	$\Delta$ Median (days)	$\Delta$ Median (%)	P-value <sup>a</sup>
All dogs (n = 186)	112	65.5	+46.5	+71	0.1234
No previous chemotherapy/ radiotherapy (n = 143)	118	65.5	+52.5	+80	0.0143

<sup>a</sup> Log rank test comparing treatments

In the sub-population, dogs without previous chemotherapy and/or radiotherapy, the impact of masitinib mesylate on time to progression was better than in the overall population. The study was not designed for TTP to support substantial evidence of effectiveness.

#### Adverse Reactions

Adverse reactions that occurred in dogs treated with masitinib more frequently than the placebo group included vomiting, diarrhea, elevated liver enzymes, alopecia, decreased appetite, neutropenia, lethargy, cough, ocular disorders, anorexia, lymphadenopathy, subcutaneous edema, azotemia, hypoalbuminemia, hypoproteinemia, elevated urine protein creatinine ratio (UPC), proteinuria, renal failure, asthenia, lipoma, anemia, hemolytic anemia, constipation, dyspnea, circulatory collapse, dehydration, hypoglycemic seizure, pleural effusion, cardiomegaly, tachycardia, syncope, intra-abdominal hemorrhage, pancreatitis, aspiration pneumonia, back pain, spinal cord compression, inability to walk, fatigue, pruritus, behavioral changes and death.

#### Conclusion

The study results suggest there is a reasonable expectation of effectiveness for the use of KINAVET-CA1 (masitinib mesylate) tablets for the treatment of Grade II or III nonresectable or recurrent (post-surgery) cutaneous mast cell tumors in dogs not previously treated by radiotherapy and/or chemotherapy except corticosteroids.

### III. TARGET ANIMAL SAFETY:

#### A. Relative Bioavailability (Bridging) Study

- a) Study Title: Relative Bioavailability Study after Single Oral Administration of a Solution and Two Different Tablet Formulations to Male Beagle Dogs, Study No. 30487 PAC
- b) Type of Study: Laboratory study
- c) Study Dates: October 2005

d) Study Director and Location: Terence Appelqvist, CIT, Evreux, France

e) General Design

Purpose of Study: To compare the bioavailability of an oral solution used in the toxicity studies to the veterinary tablet.

Study Animals: Fifteen male Beagle dogs (approximately 7 months of age) were randomly allocated to three treatment groups of 5 dogs each.

Treatment Groups: Each treatment group was treated with each of the three dosage forms (solution and two different tablet forms) in a crossover design, separated by a 7-day washout period. On the three treatment days (Days 1, 8, and 15), each treatment group received a different formulation.

Drug Administration: The three dosage forms included a veterinary tablet and another tablet formulation, each containing 100 mg masitinib base, and a solution of 2.5 mg/mL masitinib base in normal saline. Over the course of the study, each dog was treated with one veterinary tablet, the other tablet, and 40 mL of solution. Tablet administration was followed with 40 mL of tap water by syringe; the solution was administered by gavage. Dogs were fasted overnight prior to each treatment, and then fed 6 hours after dosing.

Measurements and Observations: Blood samples were collected pre-dose and at 0.5, 1, 2, 3, 4, 6, 9, 12, 16, 24, and 48 hours post-dosing. The dogs were monitored for vomiting within the first hour post-dosing, mortality, clinical signs, and body weight.

Statistical Methods: Bioequivalence was assessed using 90% confidence intervals on log transformed data.

f) Results

One dog vomited after receiving the solution, and the plasma concentration data for this dog was not included in the statistical analysis. Excessive salivation was observed in this dog and in one other dog following gavage with the solution. Excessive salivation was not reported in any dogs after administration of the tablets. The results show that the bioavailability of masitinib veterinary tablets is 18% greater than the solution formulation administered by gavage. See Table 4 below.

Table 4: Pharmacokinetic Parameters Derived from Masitinib Concentrations

Parameter	Solution Mean (SD)	Veterinary Tablet Mean (SD)	90% CL <sup>a</sup>
Dose (mg/kg)	11.3 (0.5)	11.2 (0.5)	N/A
C <sub>max</sub> (ng/mL)	819 (437)	895 (283)	113 [93, 133] <sup>c</sup>
T <sub>max</sub> (hour)	1.9 (0.9)	2.3 (0.8)	N/A
AUC <sub>0-t</sub> (hr·ng/mL) <sup>b</sup>	4746 (1566)	5701 (1934)	118 [100, 137] <sup>c</sup>
Half-life (hour)	3.4 (0.3)	3.2 (0.4)	N/A
AUC <sub>0-∞</sub> (hr·ng/mL)	4790 (1586)	5758 (1969)	N/A

<sup>a</sup> CL estimated on Log Transform data. Values listed as Mean [Lower Limit, Upper Limit].

<sup>b</sup> AUC<sub>0-t</sub> values were determined by log-linear trapezoidal rule.

<sup>c</sup> Comparison: Veterinary Tablet/Solution

- g) Conclusions for the Relative Bioavailability (Bridging) Study: Masitinib veterinary tablets are 18% more bioavailable than the masitinib solution formulation administered by gavage in the toxicity studies. In the descriptions of the toxicity studies, for ease of comparison of dose group results to the label dose, this FOI Summary provides doses comparable to KINAVET-CA1 tablet doses (i.e., 18% less than the toxicity study doses of masitinib base in solution).

#### B. 4-Week Toxicity Study

- Study Title and Number: 4-Week Toxicity Study By Oral Route (Gavage) In Beagle Dogs Followed by a 2-Week Treatment-Free Period, Study No. 24371 TSC.
- Type of Study: GLP laboratory study, toxicity study with pharmacokinetics
- Study Dates: April – May 2003
- Study Director and Location: Isabelle Gaou, CIT, Evreux, France
- General Design

**Purpose of Study:** To evaluate the potential toxicity of an oral solution of masitinib, administered daily for 4 weeks, and the potential reversibility of findings after a subsequent 2-week treatment-free recovery period.

**Study Animals:** Thirty-two Beagle dogs (approximately 6 months of age) were randomly allocated to three test item groups and one control group.



Treatment Groups:

Table 5: Treatment Group Doses for the 4-Week Toxicity Study

Treatment Group	Comparable KINAVET-CA1 Tablet Dose <sup>a</sup>	Number of Dogs
Group 1 (Control)	0 mg/kg (normal saline)	5 males and 5 females
Group 2	10.5 mg/kg	3 males and 3 females
Group 3	35.1 mg/kg	3 males and 3 females
Group 4	105.5 mg/kg	5 males and 5 females

<sup>a</sup> Masitinib was administered as a solution in saline

Drug Administration: Dogs were dosed by gavage once daily at the specified dose for 4 weeks. At the end of the treatment period, two males and two females of the control and the 35.1 mg/kg and 105.5 mg/kg groups were evaluated for a 2-week treatment-free recovery period.

Measurements and Observations: The dogs were monitored for mortality, clinical signs, body weight, food consumption, ophthalmic changes, electrocardiograph recordings, hematological, blood biochemical, bone marrow evaluation, toxicokinetics, and urinalysis. On completion of the treatment or treatment-free period, designated dogs were euthanized and underwent full macroscopic examination, designated organs were weighed and selected tissue specimens were preserved for microscopic examination.

Statistical Methods: Absolute organ weights and body weight gain (at the end of the treatment period compared to the beginning) were analyzed using an analysis of variance. The terms in the model were dose group, sex, and dose group by sex (except for testes). Variables that had baseline values measured, such as clinical pathology and heart rate, were analyzed using analysis of covariance. The terms in the model were the dose group, sex, dose group by sex, and baseline. For the 8 dogs (4 in Group 1, and 4 in Group 4) that went through the treatment-free period, only the data collected during the treatment period were used in the analysis.

f) Results

Dose related trends for clinical signs are shown in Table 6.

Table 6: Incidence of Clinical Signs in the 4-Week Toxicity Study

Clinical Sign	Group 1 (n=10)	Group 2 <sup>a</sup> (n=6)	Group 3 <sup>a</sup> (n=6)	Group 4 <sup>a</sup> (n=10)
Pallor	0	0	5	10
Soft stool to diarrhea				
Incidence	0	2	4	10
Frequency in affected dogs		1-2x/dog <sup>b</sup>	1-3x/dog	2-8x/dog
Blood-tinged feces	0	0	0	4
Vomiting or regurgitation				
Incidence	0	2	6	10
Frequency in affected dogs		2-3x/dog	4-11x/dog	12-23x/dog
Excessive salivation <sup>c</sup>				
Incidence	0	2	6	10
Frequency in affected dogs		2-3x/dog	8-18x/dog	10-20x/dog
Lethargy	0	1 (< 1 day)	0	1 (3 days)
Weight loss >5%, Day 1-28	0	0	0	4
Death	0	0	0	1 <sup>d</sup>

<sup>a</sup> Groups 2, 3, and 4 were treated with daily doses of masitinib solution comparable to KINAVET-CAI tablet doses of 10.5 mg/kg, 35.1 mg/kg, and 105.5 mg/kg, respectively.

<sup>b</sup> Frequency in affected dogs denoted as 1-2x/dog means: 1 to 2 times per dog.

<sup>c</sup> Excessive salivation was related to gavage of masitinib solution.

<sup>d</sup> The dog that became recumbent and died on Day 29 had lesions compatible with aspiration (acute esophagitis and pneumonitis).

Dose related trends in selected clinical pathology test results are shown in Table 7.

Table 7: Incidence of Selected Clinical Pathology Results<sup>a</sup> in the 4-Week Toxicity Study

Variable	Group 1 (n=10)	Group 2 (n=6)	Group 3 (n=6)	Group 4 (n=10)
Anemia incidence and severity <sup>b</sup>	0	1 mild	1 moderate 3 mild	1 moderate 4 mild
Neutropenia incidence and severity <sup>c</sup>	0	1 mild	2 moderate 4 mild	1 moderate 2 mild
Hypoalbuminemia incidence and severity <sup>d</sup>	0	0	2 mild	2 moderate 7 mild
Elevated fibrinogen or APTT (activated partial thromboplastin time)	0	0	0	1 fibrinogen 1 APTT
Elevated AST & ALT <sup>e</sup>	0	0	0	1 mild
Proteinuria reported in dogs with no proteinuria at baseline <sup>f</sup>	0	0	1 low	1 moderate 5 low
Hematuria reported in dogs with no hematuria at baseline <sup>g</sup>	0	0	0	1 high 1 moderate 2 low

<sup>a</sup> Results at the end of the 4-week treatment period

<sup>b</sup> Anemia severity: mild = hemoglobin (Hb) <12-10 g/dL, moderate = Hb <10-8 g/dL

<sup>c</sup> Neutropenia severity: mild =  $2.0-3.0 \times 10^3 \mu\text{L}$ , moderate =  $1.0-1.9 \times 10^3 \mu\text{L}$

<sup>d</sup> Hypoalbuminemia severity: mild = 2.1-2.7 g/dL, moderate = 1.5-2.0 g/dL

<sup>e</sup> Elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were mild; both were less than 2 times the upper limit of the normal range.

<sup>f</sup> Proteinuria by dipstick test: low = 0.3 g/L, moderate = 1.0 g/L, high =  $\geq 3.0 \text{ g/L}$ . In these cases, proteinuria occurred in urine samples that did not have red or white blood cells on microscopic examination of the urine sediment.

<sup>g</sup> Hematuria was determined by dipstick test. Bilirubinuria was also increased in Group 4.

Statistically significant results at the end of the treatment period are shown in Table 8.

Table 8: Statistically Significant Results in the 4-Week Toxicity Study <sup>a</sup>

Variables	Treated vs. Control
Body weight gain	Group 4 < Group 1
Heart Rate	Group 4 > Group 1
<u>Hematology</u>	
Red Blood Cell Count (RBC)	Groups 2, 3 & 4 < Group 1
Hemoglobin (Hb)	Groups 2, 3 & 4 < Group 1
Packed Cell Volume (PCV)	Groups 2, 3 & 4 < Group 1
MCV <sup>b</sup>	Groups 2, 3 & 4 < Group 1
MCHC <sup>b</sup>	Groups 3 & 4 > Group 1
Neutrophil Count	Groups 2, 3 & 4 < Group 1
White Blood Cell Count (WBC)	Groups 2, 3 & 4 < Group 1
Eosinophil Count	Groups 3 & 4 < Group 1
<u>Coagulation</u>	
Fibrinogen	Group 4 > Group 1
Activated Partial Thromboplastin Time (APTT)	Group 4 > Group 1
<u>Biochemistry</u>	
Total protein	Groups 3 and 4 < Group 1
Albumin	Groups 3 and 4 < Group 1
Calcium	Groups 3 and 4 < Group 1
Creatine Kinase	Groups 3 and 4 > Group 1
Chloride	Groups 3 and 4 > Group 1
Glucose	Groups 3 and 4 > Group 1
Urea Nitrogen (BUN)	Group 4 > Group 1
Alkaline Phosphatase (ALP)	Group 4 > Group 1
Alanine Aminotransferase (ALT)	Group 4 > Group 1
<u>Absolute Organ Weight</u>	
Thymus Weight	Group 4 < Group 1

<sup>a</sup> Results at the end of the 4-week treatment period. p-values < 0.1

<sup>b</sup> Decreased MCV (mean corpuscular volume) and increased MCHC (mean corpuscular hemoglobin concentration) are consistent with a non-regenerative anemia.

Histopathologic lesions primarily involved the liver, bone marrow, and lymphatic tissue. Dose related trends in histopathology results are shown in Table 9.

Table 9: Incidence of Selected Histopathology Results<sup>a</sup> in the 4-Week Toxicity Study

Histopathology	Incidence and Severity			
	Group 1 (n=6)	Group 2 (n=6)	Group 3 (n=6)	Group 4 (n=6)
Vacuolated hepatocytes <sup>b</sup>	1 minimal	0	1 minimal	1 marked 1 moderate
Vacuolated Kupffer cells <sup>b</sup>	0	0	1 slight 3 minimal	1 marked 2 moderate 2 slight 1 minimal
Brownish pigment laden Kupffer cells	0	0	2 minimal	5 minimal
Bile canicular plugs	0	0	4 minimal	3 slight 3 minimal
Bone marrow hypo-cellularity <sup>c</sup>	0	0	1 marked 3 moderate 2 slight	2 marked 2 moderate 2 slight
Bone marrow lipoid tissue <sup>c</sup>	6 minimal	1 slight 5 minimal	4 marked 2 moderate	4 marked 2 moderate
Lymphoid depletion of the thymus	1 moderate 1 slight	4 minimal	1 slight 3 minimal	2 marked 1 slight 2 minimal
Foamy macrophages in the mesenteric lymph node (LN)	0	0	5 minimal	2 slight 3 minimal
Decreased germinal centers in the mandibular LN	0	0	0	2 slight
Lymphoid depletion of the spleen	0	0	0	1 slight
Histiocytosis of the spleen	0	0	0	2 slight 2 minimal
Foamy alveolar (lung) macrophages	0	3 minimal	2 minimal	3 slight 2 minimal
Acute esophagitis	0	0	1 slight	1 marked 1 moderate

<sup>a</sup> Results of dogs necropsied at the end of the 4-week treatment period

<sup>b</sup> Of the six Group 4 dogs necropsied at the end of the 4-week treatment period, three had grossly enlarged livers with moderate to marked vacuolization of hepatocytes and/or Kupffer cells on histopathology.

<sup>c</sup> Bone marrow histopathology is consistent with bone marrow cytology on dogs necropsied at the end of the 4-week treatment period, which showed a dose dependent increase in the myeloid to erythroid ratio.

On completion of the 2-week recovery period, a partial reversibility was noted in animals from Group 4. See Table 10.

Table 10: Clinical Findings at the End of the 2-Week Recovery Period

Findings	Incidence	
	Group 1 (n=4)	Group 4 (n=4)
Pallor	0	4
Anemia, mild	0	1
Regenerative anemia, mild (increased reticulocyte count)	0	4
Increased platelet count, mild	0	1
Hypoalbuminemia, mild	0	1
Grey/green colored livers at necropsy with bile canaliculi plugs on histopathology	0	3
Liver brownish pigment laden macrophages, minimal	0	3
Liver brownish pigment laden Kupffer cells, minimal	0	1
Vacuolated Kupffer cells, minimal	0	1
Enlarged spleen	0	4

Plasma Levels of Masitinib: On the first day of dosing, plasma masitinib exposure increased with dose, but the increases in  $C_{max}$  and AUC were less than proportional over the three doses tested. This study tested doses comparable to KINAVET-CA1 tablet doses of 10.5 mg/kg (Group 2), 35.1 mg/kg (Group 3), and 105.5 mg/kg (Group 4). Inter-animal coefficients of variation in  $C_{max}$  ranged 8 to 28% and inter-animal coefficients of variation in AUC ranged 9 to 70%.

After 28 days of dosing, the increases in  $C_{max}$  and AUC were nearly proportional across the Group 2 and 3 dose range because plasma masitinib accumulation was observed (at least 26%) in Group 3. Inter-animal coefficients of variation in  $C_{max}$  ranged 14 to 19% and inter-animal coefficients of variation in AUC ranged 14 to 32%. Significant plasma masitinib accumulation ( $\geq 46\%$  on average) was observed in Group 4 after 28 days. A gender effect was not noted.

- g) Conclusions for the 4-Week Toxicity Study: Transient and occasional vomiting, soft feces, and lethargy occurred at a dose comparable to 0.7X the maximum label dose of 15.0 mg/kg/day. At doses comparable to 2.3X and 7X the maximum label dose, dogs had a dose-dependent increase in the incidence and severity of gastrointestinal signs (vomiting, diarrhea, blood in the feces), bone marrow suppression (hypocellularity, non-regenerative anemia, pallor, and neutropenia), proteinuria and hypoalbuminemia without associated kidney lesions on histopathology, liver abnormalities (mildly increased liver enzymes, histopathologic lesions), lymphatic tissue toxicity (lymphoid depletion and other

histopathologic lesions), and increased coagulation values. Treatment related effects were partially reversible after a 2-week treatment-free recovery period.

### C. 13-Week Toxicity Study

- a) Study Title and Number: 13-Week Toxicity Study By Oral Route (Gavage) In Beagle Dogs Followed by a 4-Week Treatment-Free Period, Study No. 24373 TCC
- b) Type of Study: GLP laboratory study
- c) Study Dates: June – October 2003
- d) Study Director and Location: Isabelle Gaou, CIT, Evreux, France
- e) General Design

Purpose of Study: To evaluate the potential toxicity of an oral solution of masitinib, administered daily for 13 weeks, and the potential reversibility of findings after a subsequent 4-week treatment-free recovery period.

Study Animals: Thirty-two Beagle dogs (approximately 6 months of age) were randomly allocated to three test item groups and one control group. One Group 4 dog died on Day 8 and was replaced by another dog.

#### Treatment Groups:

Table 11: Treatment Group Doses for the 13-Week Toxicity Study

Treatment Group	Comparable KINAVET-CA1 Tablet Dose <sup>a</sup>	Number of Dogs
Group 1 (Control)	0 mg/kg(normal saline)	5 males and 5 females
Group 2	3.5 mg/kg	3 males and 3 females
Group 3	10.5 mg/kg	3 males and 3 females
Group 4	35.1 mg/kg	5 males and 5 females

<sup>a</sup> Masitinib was administered as a solution in saline

Drug Administration: Dogs were dosed by gavage once daily at the specified dose for 13 weeks. At the end of the treatment period, two males and two females of the control and high-dose groups were evaluated for a 4-week treatment-free recovery period.

**Measurements and Observations:** The dogs were monitored for mortality, clinical signs, body weight, food consumption, ophthalmology examinations, electrocardiograph recordings, hematological, blood biochemical investigations, toxicokinetics, and urinalysis. On completion of the treatment or treatment-free period, designated dogs were euthanized and underwent full macroscopic examination, designated organs were weighed and selected tissue specimens were preserved for microscopic examination.

**Statistical Methods:** Absolute organ weights and body weight gain (at the end of the treatment period compared to the beginning) were analyzed using an analysis of variance. The terms in the model were dose group, sex, and dose group by sex (except for testes). Variables that had baseline values measured, such as clinical pathology and heart rate, were analyzed using analysis of covariance. The terms in the model were the dose group, sex, dose group by sex, and baseline. For the 8 dogs (4 in Group 1, and 4 in Group 4) that went through the treatment-free period, only the data collected during the treatment period were used in the analysis.

#### f) Results

Dose related trends in clinical signs are shown in Table 12.

Table 12: Incidence of Clinical Signs in the 13-Week Toxicity Study

Clinical Sign	Group 1 (n=10)	Group 2 <sup>a</sup> (n=6)	Group 3 <sup>a</sup> (n=6)	Group 4 <sup>a</sup> (n=11)
Pallor	0	0	0	9
Soft stool to diarrhea				
Incidence	5	4	1	7
Frequency in affected dogs	1-5x/dog	1-3x/dog	3x/dog	2-7x/dog
Vomiting or regurgitation				
Incidence	0	0	3	9
Frequency in affected dogs			1-3x/dog	1-4x/dog
Excessive salivation <sup>b</sup>				
Incidence	0	1	4	10
Frequency in affected dogs		1x/dog	1-6x/dog	≥ 20x/dog
Lethargy or weakness	0	0	1	2
Erythema of muzzle	0	0	1	0
Death	0	0	0	1 <sup>c</sup>

<sup>a</sup> Groups 2, 3, and 4 were treated with daily doses of masitinib solution comparable to KINAVET-CAI tablet doses of 3.5 mg/kg, 10.5 mg/kg, and 35.1 mg/kg, respectively.

<sup>b</sup> Excessive salivation was related to gavage of masitinib solution.

<sup>c</sup> The Group 4 dog died shortly after dosing on Day 8 had lesions compatible with aspiration (reddish colored lungs and foamy contents in the trachea and lungs). She was replaced with another female that underwent all procedures 8 days after the rest of the dogs in her group.



Dose related trends in selected clinical pathology test results are shown in Table 13.

Table 13: Incidence of Selected Clinical Pathology Results<sup>a</sup> in the 13-Week Toxicity Study

Variable	Incidence and Severity			
	Group 1 (n=10)	Group 2 (n=6)	Group 3 (n=6)	Group 4 (n=6)
Anemia <sup>b</sup>	0	0	1 mild	1 moderate 6 mild
Neutropenia <sup>c</sup>	0	0	0	1 moderate 6 mild
Hypoalbuminemia <sup>d</sup>	0	0	0	2 mild
Elevated fibrinogen or APTT (activated partial thromboplastin time)	0	0	0	1 fibrinogen 1 APTT
Elevated alkaline phosphatase (ALP) <sup>e</sup>	0	0	0	1 mild
Elevated blood glucose <sup>f</sup>	0	0	0	1 moderate

<sup>a</sup> Results during or at the end of the 13-week treatment period

<sup>b</sup> Anemia severity: mild = Hb <12-10 g/dL, moderate = Hb <10-8 g/dL

<sup>c</sup> Neutropenia severity: mild =  $2.0-3.0 \times 10^3 \mu\text{L}$ , moderate =  $1.0-1.9 \times 10^3 \mu\text{L}$

<sup>d</sup> Hypoalbuminemia severity: mild = 2.1-2.7 g/dL, moderate = 1.5-2.0 g/dL

<sup>e</sup> ALP elevation was mild, less than 2 times the upper limit of the normal range

<sup>f</sup> Glucose was moderately elevated, at 190 mg/dL

Statistically significant results at the end of the treatment period are shown in Table 14.

Table 14: Statistically Significant Results in the 13-Week Toxicity Study <sup>a</sup>

Variables	Treated vs. Control
<u>Hematology</u>	
Red Blood Cell Count (RBC)	Groups 3 & 4 < Group 1
Hemoglobin (Hb)	Groups 3 & 4 < Group 1
Packed Cell Volume (PCV)	Groups 3 & 4 < Group 1
MCV <sup>b</sup>	Groups 3 & 4 > Group 1
MCHC <sup>b</sup>	Groups 3 & 4 < Group 1
Neutrophil Count	Group 4 < Group 1
White Blood Cell Count (WBC)	Group 4 < Group 1
Eosinophil Count	Group 4 < Group 1
Platelet Count	Group 4 > Group 1
<u>Coagulation</u>	
Fibrinogen	Group 4 > Group 1
Activated Partial Thromboplastin Time (APTT)	Groups 3 & 4 > Group 1
<u>Biochemistry</u>	
Albumin	Group 4 < Group 1
Calcium	Group 4 < Group 1
Potassium	Group 4 > Group 1
Chloride	Group 4 > Group 1
Alkaline Phosphatase (ALP)	Group 4 > Group 1
Alanine Aminotransferase (ALT)	Group 4 > Group 1
<u>Absolute Organ Weight</u>	
Liver Weight	Groups 3 & 4 > Group 1

<sup>a</sup> Results at the end of the 13-week treatment period, p-values < 0.1

<sup>b</sup> Increased MCV (mean corpuscular volume) and decreased MCHC (mean corpuscular hemoglobin concentration) are opposite from the 4-week toxicity study results (Study No. 24371 TSC).

Histopathologic lesions primarily involved the liver, gall bladder, bone marrow, and lungs. Dose related trends in histopathology results are shown in Table 15.

Table 15: Incidence of Selected Histopathology Results<sup>a</sup> in the 13-Week Toxicity Study

Lesions	Incidence and Severity			
	Group 1 (n=6)	Group 2 (n=6)	Group 3 (n=6)	Group 4 (n=6)
Hepatocellular hypertrophy	0	0	0	2 slight 4 minimal
Brownish pigment laden Kupffer cells	0	0	0	1 slight
Gall bladder cystic epithelial hyperplasia	0	0	0	2 slight
Bone marrow lipid tissue	1 moderate 2 slight 1 minimal	1 slight 3 minimal	1 moderate 1 slight 3 minimal	3 marked 2 minimal
Chronic interstitial pneumonitis	1 minimal	0	0	2 moderate

<sup>a</sup> Results of dogs necropsied at the end of the 13-week treatment period

On completion of the 4-week recovery period, the adverse findings previously recorded for dogs in Group 4 were no longer observed.

Plasma Levels of Masitinib: On the first day of dosing plasma masitinib exposure increased with dose and appeared to be dose proportional over the three doses tested. This study tested doses comparable to KINAVET-CA1 tablet doses of 3.5 mg/kg (Group 2), 10.5 mg/kg (Group 3), and 35.1 mg/kg (Group 4). Inter-animal coefficients of variation in  $C_{max}$  ranged 35 to 56% and inter-animal coefficients of variation in AUC ranged 38 to 59%.

After 13 weeks of daily dosing increases in  $C_{max}$  and AUC were more than dose proportional for Group 3 and Group 4 compared to Group 2. However,  $C_{max}$  and AUC values were proportional in Groups 3 and 4. Inter-animal coefficients of variation in  $C_{max}$  ranged 19 to 95% and inter-animal coefficients of variation in AUC ranged 23 to 101%. Plasma masitinib exposure accumulation was variable (20 to > 200 %) in Groups 3 and 4 after 13 weeks of daily dosing. A gender effect was not noted.

- g) Conclusions for the 13-Week Toxicity Study: Transient and occasional vomiting, muscle weakness, erythema of the muzzle, and mild anemia occurred at a dose comparable to 0.7X the maximum label dose of 15.0 mg/kg/day. At a dose comparable to 2.3X the maximum label dose, dogs had vomiting, diarrhea, lethargy, and mild hypoalbuminemia. The dogs also had evidence of bone marrow suppression (increased lipid tissue in the bone marrow, anemia, pallor,

and neutropenia), liver abnormalities (mildly increased liver enzymes, histopathologic lesions), and increased coagulation values. Treatment related effects were no longer observed (reversed) after a 4-week treatment-free recovery period.

#### D. 39-Week Toxicity Study

- a) Study Title and Number: 39-Week Toxicity Study By Oral Route (Gavage) In Beagle Dogs, Study No. 26100 TCC.
- b) Type of Study: GLP laboratory study
- c) Study Dates: August 2003 – May 2004.
- d) Study Director and Location: Isabelle Gaou, CIT, Evreux, France
- e) General Design

Purpose of Study: To evaluate the potential toxicity and pharmacokinetics of an oral solution of masitinib, administered daily for 39 weeks.

Study Animals: Thirty-two Beagle dogs (approximately 7 months of age) were randomly allocated to three test item groups and one control group of 4 males and 4 females each.

#### Treatment Groups:

Table 16: Treatment Group Doses for the 39-Week Toxicity Study

Treatment Group	Comparable KINAVET-CA1 Tablet Dose <sup>a</sup>	Number of Dogs
Group 1 (Control)	0 mg/kg (normal saline)	4 males and 4 females
Group 2	2.1 mg/kg	4 males and 4 females
Group 3	7.0 mg/kg	4 males and 4 females
Group 4	20.9 mg/kg	4 males and 4 females

<sup>a</sup> Masitinib was administered as a solution in saline

Drug Administration: Dogs were dosed by gavage daily at the specified level for 39 weeks.

Measurements and Observations: The dogs were monitored for mortality, clinical signs, body weight, food consumption, ophthalmology examinations, electrocardiograph recordings, hematological, blood biochemical investigations, toxicokinetics, and urinalysis. On completion of the treatment period, the dogs

were euthanized and underwent full macroscopic examination, designated organs were weighed and selected tissue specimens were preserved for microscopic examination.

Statistical Methods: Absolute organ weights and body weight gain (at the end of the study compared to the beginning) were analyzed using an analysis of variance. The terms in the model were dose group, sex, and dose group by sex (except for testes). Variables which were measured multiple times during the study (including baseline measurements), such as clinical pathology and heart rate, were analyzed using a repeated measures analysis of covariance. The terms in the model were dose group, study day, sex, all their two- and three-way interactions, and baseline.

f) Results

Mortality: One Group 4 female was euthanized prematurely on Day 225 (Week 33). During the weeks preceding euthanasia, she developed a swollen abdomen due to ascites, emaciated appearance, pallor, decreased appetite, lethargy, loss of balance, tremors, lateral recumbency, severe anemia, marked thrombocytosis, lymphopenia, increased APTT and fibrinogen, severe hypoalbuminemia and hypoproteinemia, increased blood urea nitrogen and creatine kinase, severe proteinuria, hematuria without red cells, and decreased urine pH. Histopathology findings included edema in the pericardium, thymus, subcutaneous tissue, pancreas and adjacent lymph nodes, and severe lymphoid depletion in the thymus.

Dose related trends in clinical signs are shown in Table 17.

Table 17: Incidence of Clinical Signs in the 39-Week Toxicity Study

Clinical Sign	Group 1 (n=8)	Group 2 <sup>a</sup> (n=8)	Group 3 <sup>a</sup> (n=8)	Group 4 <sup>a</sup> (n=8)
Pallor	0	0	1	8
Soft stool to diarrhea				
Incidence	4	0	4	6
Frequency in affected dogs	1-5x/dog		1-2x/dog	1-3x/dog
Vomiting or regurgitation				
Incidence	1	1	2	6
Frequency in affected dogs	1x	1x	1-4x/dog	1-3x/dog
Excessive salivation <sup>b</sup>				
Incidence	1	3	8	8
Frequency in affected dogs	1x	1-3x/dog	1-12x/dog	≥ 68x/dog
Lethargy	0	0	2	3
Lateral recumbency	0	0	0	2
Hind leg stiffness	0	0	0	1
Erythema of the neck	0	0	1	2
Depigmentation of eyelids	0	0	0	1
Reported to be emaciated in the last 3 weeks of the study	1	2	0	4
Death	0	0	0	1 <sup>c</sup>

<sup>a</sup> Groups 2, 3, and 4 were treated with daily doses of masitinib solution comparable to KINAVET-CA1 tablet doses of 2.1 mg/kg, 7.0 mg/kg, and 20.9 mg/kg, respectively.

<sup>b</sup> Excessive salivation was related to gavage of masitinib solution.

<sup>c</sup> The dog that was euthanized in Week 33 is described above.

Dose related trends in selected clinical pathology test results are shown in Table 18.

Table 18: Incidence of Selected Clinical Pathology Results<sup>a</sup> in the 39-Week Toxicity Study

Variable	Group 1 (n=8)	Group 2 (n=8)	Group 3 (n=8)	Group 4 (n=8)
Anemia <sup>b</sup> : Incidence and Severity	0	0	2 mild	1 very severe 6 mild
Neutropenia <sup>c</sup> : Incidence and Severity	0	0	0	4 mild
Hypoalbuminemia <sup>d</sup> : Incidence and Severity	0	0	0	1 severe 2 mild
Elevated Fibrinogen or APTT (Activated partial thromboplastin time)	0	0	0	2 Fibrinogen 1 APTT
Proteinuria reported in dogs with no proteinuria at baseline <sup>e</sup>	0	1 low	3 low	2 high 3 low

<sup>a</sup> The worst result reported for each dog during the 39-week study

<sup>b</sup> Anemia: mild = Hb <12-10 g/dL. The dog with very severe anemia had a Hb of 3.9 g/dL prior to euthanasia in Week 33.

<sup>c</sup> Neutropenia: mild = 2.0-3.0 x 10<sup>3</sup>  $\mu$ L, moderate = 1.0-1.9 x 10<sup>3</sup>  $\mu$ L

<sup>d</sup> Hypoalbuminemia: mild = 2.1-2.7 g/dL, moderate = 1.5-2.0 g/dL, severe < 1.5 g/dL

<sup>e</sup> Proteinuria by dipstick test: low = 0.3 g/L, moderate = 1.0 g/L, high =  $\geq$  3.0 g/L. In these cases, proteinuria occurred in urine samples that did not have red or white blood cells on microscopic examination of the urine sediment.

Statistically significant results are shown in Table 19.

Table 19: Statistically Significant Results in the 39-Week Toxicity Study <sup>a</sup>

Variables	Treated vs. Control
<u>Dose group*day significant for hematology and coagulation</u>	
RBC	Groups 3 & 4 < Group 1 at Weeks 13, 25, and 38
Hemoglobin	Groups 3 & 4 < Group 1 at Weeks 13, 25, and 38
PCV	Groups 3 & 4 < Group 1 at Weeks 13, 25, and 38
MCV <sup>b</sup>	Group 3 > Group 1 at Week 13 Group 4 > Group 1 at Weeks 13, 25, and 38
Neutrophil Count	Group 3 < Group 1 at Weeks 25 and 38 Group 4 < Group 1 at Weeks 13, 25, and 38
Eosinophil Count	Group 4 < Group 1 at Week 38
<u>Dose group main effect significant for hematology and coagulation</u>	
MCHC <sup>b</sup>	Groups 3 & 4 < Group 1
WBC	Group 4 < Group 1
Platelets	Group 4 > Group 1
APTT	Group 4 > Group 1
Prothrombin time	Group 4 > Group 1
<u>Dose group main effect significant for biochemistry</u>	
Total protein	Groups 3 & 4 < Group 1
Albumin	Group 4 < Group 1
Calcium	Group 4 < Group 1
<u>Dose group*day significant for biochemistry</u>	
Sodium	Groups 3 & 4 < Group 1 at Week 38
Glucose	Group 4 > Group 1 at Weeks 13 and 25
<u>Dose group main effect significant for absolute organ weight</u>	
Heart Weight <sup>c</sup>	Groups 2, 3 & 4 > Group 1

<sup>a</sup> p-values < 0.1

<sup>b</sup> Increased MCV (mean corpuscular volume) and decreased MCHC (mean corpuscular hemoglobin concentration) are consistent with the 13-week study results, but the opposite of the 4-week study results.

<sup>c</sup> Mean absolute organ weights excluding the Group 4 female euthanized at Week 33



Histopathologic lesions primarily involved the spleen, liver, bone marrow, and lymphatic tissue. Dose related trends in histopathology results are shown in Table 20.

Table 20: Incidence of Selected Histopathology Results in the 39-Week Toxicity Study

Lesions	Incidence and Severity			
	Group 1 (n=8)	Group 2 (n=8)	Group 3 (n=8)	Group 4 (n=8)
Generalized edema	0	0	0	1 <sup>a</sup>
Increased iron deposits in the spleen (hemosiderosis)	1 slight 6 minimal	5 slight 3 minimal	5 moderate 2 slight 1 minimal	4 marked 4 moderate
Brownish pigment laden Kupffer cells <sup>b</sup>	0	0	2 minimal	1 moderate 3 slight 3 minimal
Liver positive for iron	0	1 minimal	2 minimal	3 minimal
Mandibular lymph node positive for iron	0	2 minimal	4 minimal	5 minimal
Bone marrow lipoid tissue	3 slight 5 minimal	3 moderate 3 slight 2 minimal	2 marked 3 moderate 2 slight 1 minimal	4 marked 4 moderate
Lymphoid depletion of the thymus <sup>c</sup>	1 moderate 5 slight 2 minimal	3 moderate 3 minimal	4 moderate 2 minimal	1 massive 1 marked 2 moderate 2 slight 2 minimal
Vacuolated seminiferous tubules and oligospermia	0/4 males	0/4 males	0/4 males	2/4 males (slight to moderate)

<sup>a</sup> The dog that was euthanized at Week 33 had ascites, subcutaneous edema, and edema of the thymus, pancreas and associated lymph nodes.

<sup>b</sup> One Group 4 male had an enlarged grey/green colored liver on gross necropsy.

<sup>c</sup> On gross necropsy, small thymus glands were reported in 2/8 Group 1, 1/8 Group 2, 2/8 Group 3, and 4/8 Group 4 dogs.

**Plasma Levels of Masitinib:** On the first day of dosing, the plasma masitinib exposure increased with dose; based on the Group 2 dose the increase in  $C_{max}$  and AUC values was more than dose proportional after the first dose. However, the increases in  $C_{max}$  and AUC appear to be proportional across the Group 3 and 4 dose range. This study tested doses comparable to KINAVET-CA1 tablet doses of 2.1 mg/kg (Group 2), 7.0 mg/kg (Group 3), and 20.9 mg/kg (Group 4). Inter-animal coefficients of variation in  $C_{max}$  ranged 20 to 39% and inter-animal coefficients of variation in AUC ranged 25 to 41%.

After 39 weeks of exposure the  $C_{max}$  and AUC values at higher doses appear to decrease compared to the Group 2 dose because exposure accumulation was

observed in Group 2. Exposure accumulation was not observed in Groups 3 or 4. This observation is in agreement with the results for Group 2 in the 4-week toxicity study, which was treated with a dose comparable to a KINAVET-CA1 tablet dose of 10.5 mg/kg. Inter-animal coefficients of variation in  $C_{max}$  ranged 24 to 59% and inter-animal coefficients of variation in AUC ranged 23 to 38%. A gender effect was not noted.

- g) Conclusions for the 39-Week Toxicity Study: Vomiting, lethargy, erythema of the neck, mild anemia, proteinuria, hemosiderosis of the spleen, and increased lipid tissue in the bone marrow occurred at a dose comparable to 0.5X the maximum label dose of 15.0 mg/kg/day. At a dose comparable to 1.4X the maximum label dose, a dog was euthanized because of severe anemia, hypoproteinemia, proteinuria, pericardial effusion, ascites, emaciated appearance, and lateral recumbency. In that dose group, masitinib toxicity was characterized by gastrointestinal signs (vomiting, diarrhea), general signs (lethargy, hind leg stiffness, erythema of the neck), bone marrow suppression (increased lipid tissue in the bone marrow, anemia, pallor, and neutropenia), evidence of red blood cell sequestration (hemosiderosis of the spleen), proteinuria and hypoalbuminemia without associated kidney lesions on histopathology, liver abnormalities (histopathologic lesions), lymphatic tissue toxicity (lymphoid depletion), and increased coagulation values.

#### **IV. HUMAN FOOD SAFETY:**

This drug is intended for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

#### **V. USER SAFETY:**

The product labeling contains the following information regarding safety for humans handling, administering, or exposed to KINAVET-CA1:

**NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.** Children should not come into contact with KINAVET-CA1. Keep children away from feces, urine, or vomit of treated dogs.

To avoid exposure to drug, wash hands with soap and water after administering KINAVET-CA1 and wear protective gloves to prevent contact with feces, urine, vomit, and broken or crushed KINAVET-CA1 tablets. Place all waste material in a plastic bag and seal before general disposal. If eyes are accidentally exposed to the drug, rinse eyes with water immediately. In case of accidental ingestion by a person, seek medical advice immediately, show the package insert or label to the physician.

Pregnant women, women who may become pregnant, or nursing mothers should pay special attention to these handling precautions (see handling instructions above). KINAVET-CA1 may harm an unborn baby (cause birth defects). For pregnant and nursing women, accidental ingestion of KINAVET-CA1 may have adverse effects on pregnancy or the nursing baby.

## **VI. AGENCY CONCLUSIONS:**

The data submitted in support of this application satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act. The data demonstrate that KINAVET-CA1, when used according to the label, is safe and has a reasonable expectation of effectiveness for the treatment of recurrent (post-surgery) or nonresectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and/or chemotherapy except corticosteroids.

### **A. Marketing Status:**

KINAVET-CA1 is conditionally approved for one year from the date of approval and is annually renewable for up to four additional one-year terms.

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to properly diagnose mast cell tumors and to monitor safe use of the product, including treatment of any adverse reactions.

### **B. Exclusivity:**

KINAVET-CA1 in the dosage form and for the intended uses conditionally approved by FDA under application number 141-308 qualifies for seven years of exclusive marketing rights beginning as of the date of conditional approval. This new animal drug qualifies for exclusive marketing rights under section 573(c) of the Federal Food, Drug, and Cosmetic Act (the act) because it has been declared a designated new animal drug by FDA under section 573(a) of the act.

### **C. Patent Information:**

KINAVET-CA1 is under the following U.S. patent numbers:

<u>U.S. Patent Number</u>	<u>Date of Expiration</u>
7,423,055	August 1, 2023

For current information on patents, see the Animal Drugs @ FDA database (formerly the Green Book) on the FDA CVM internet website.

**VII. ATTACHMENTS:**

Labeling:  
Package Insert  
Client Information Sheet

# EXHIBIT H



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

INAD 011206 A-0000

AB Science  
Attention: Anne-Virginie Eggimann, M.Sc.  
Consultant  
38 rue Vauthier  
92100 Boulogne  
France

MAR 11 2004

Dear Ms. Eggimann:

We refer to your submission dated November 24, 2003, (A-0000), wherein you requested an Investigational New Animal Drug (INAD) exemption for the use of AB1010. The drug product is proposed for the treatment of mast cell tumors in dogs. Your submission also requested a presubmission conference to discuss the development of your product in the United States. Under cover letter dated January 5, 2004, (T-0001) you submitted a request for a categorical exclusion from preparing an environmental assessment.

For administrative purposes, we have assigned you INAD number 011206 for the use of AB1010 in canines. Please refer to this number in all drug shipments and correspondence concerning the drug while it is in the investigational stage. Future correspondence regarding this submission to your INAD file should be identified by the submission's correspondence date and our file number, INAD 011206 A-0000 and submitted directly to the Document Control Unit (HFV-199).

Please find enclosed CVM's minutes from the presubmission conference, which took place on December 18, 2003.

Your claim for the investigational use of AB1010 falls within the categorical exclusion in 21 CFR 25.33(e). Your submission states that to your knowledge, no extraordinary circumstances exist which may significantly affect the human environment. Therefore, neither an environmental assessment (EA) nor an environmental impact statement is required. This categorical exclusion from preparation of an EA and an Environmental Impact Statement does not relieve you of the responsibility for determining and meeting all Federal, State, and local environmental and occupational laws and regulations that apply to the manufacturing, use, and disposal of the investigational drugs.

Prior to shipment of the new animal drug for clinical tests in animals, you must submit in triplicate a "Notice of Claimed Investigational Exemption for a New Animal Drug", in accordance with 21 CFR 511.1(b)(4).

Investigational labeling should be affixed to your investigational drug product prior to shipment for studies conducted under 21 CFR 511.1(a) or (b), as appropriate.

If you have any questions or if you need further assistance, please contact, Elizabeth A. Luddy, Leader, Companion and Wildlife Team. The telephone number is (301) 827-7540.

Sincerely yours,



Melanie R. Berson, DVM  
Director  
Division of Therapeutic Drugs  
for Non-Food Animals  
Office of New Animal Drug Evaluation  
Center for Veterinary Medicine

Enclosure

I-011206-A-0000

AB1010

Canine

AB Science

38 rue Vauthier

92100 Boulogne

France

December 18, 2003

**Memorandum of Presubmission Conference  
December 18, 2003, 1 – 3 pm**

**Attendees:**

**CVM:**

Melanie Berson, HFV-110  
Elizabeth Luddy, HFV-112  
Lisa Troutman, HFV-112  
Douglass Oeller, HFV-112  
Anna Nevius, HFV-105  
Marilyn Martinez, HFV-130  
June Liang, HFV-143  
Glen Ghiorghis, HFV-143

**AB Science**

Alain Moussy  
Olivier Hermine  
Des Curran  
Philippe Reginault  
Laurent Guy  
Marie-Paul Lachaud Lefay – ICON  
Leland Vickers – ICON  
Anne-Virgine Eggimann – Consultant  
Emmanuelle Voisin – Consultant

**Background:**

The sponsor provided background information regarding the incidence of Mast Cell Tumors (MCT) in dogs. The histological grading system and survival data associated with the different grades was discussed.

**Drug Characteristics:**

The drug is referred to by two different names. AB1003 is the free base form of the drug. It is the drug referenced for the dosage (i.e., 12.5 mg/kg refers to AB1003). AB1010 is the salt form of the drug and is the final market formulation.

The drug is selective to c-kit and PDGF-beta. It does not interact with other tyrosine kinases thereby possibly reducing toxicity. The sponsor has not encountered any



evidence that there is any multi-drug resistance developed after long-term administration of the drug. There is evidence to suggest that it protects against developing resistance in human CML if there is continual pressure on the cells.

The presence of c-kit varies between patients. However, if c-kit is present, it will be in all cells within a MCT because c-kit is the cause of the mutation creating the tumor.

**Effectiveness:**

The sponsor is planning to conduct a multi-location, uncontrolled field study. The study will enroll 110 dogs with either Grade II or Grade III MCTs with or without previous treatments. Dogs may be enrolled with metastases at the discretion of the investigator. It will be conducted at 24 locations including 12 in the United States, five in the United Kingdom, two in the Netherlands, two in Germany, two in France and one in Slovenia. Two thirds of the cases will come from the United States and the remaining one third from the European countries. Locations in the United States will be with board certified oncologists.

CVM questioned whether a central laboratory will perform the histopathology and the clinical chemistry. The sponsor stated that many of the dogs will have had histopathology conducted prior to consideration for inclusion into the study. If possible, the sponsor will obtain histopathology slides to confirm the diagnosis and grading. It would be very difficult to provide a central pathologist for the study. CVM recommended that the sponsor should address the comparability of the scoring from different pathologists in the protocol. Clinical chemistry analysis will be conducted at a central laboratory in the United States.

CVM strongly suggested the sponsor submit the protocol for review to obtain protocol concurrence prior to starting the study. A dosage rationale should be included with the protocol along with scientific justification and rationale for using complete response (CR) + partial response (PR) > 20% for the success criteria. Scientific justification for conducting an uncontrolled study should also be included. Scientific literature from peer reviewed journals or similar sources, documenting the course of disease if untreated should be utilized to justify a historical control.

CVM suggested that if the sponsor was interested, they should submit a second protocol for extended use. It would allow dogs enrolled in the field study to continue receiving drug after the pivotal field study has been completed.

The sponsor presented their proof of concept. A 6 year old Chow Chow in South Africa had two Grade III MCTs with lymph node involvement. The dog was administered 5 mg/kg BID for 63 days. At the end of 63 days, there was no evidence of MCT's or lymph node involvement.

The sponsor asked if they could stop the study if 17 successes were seen after enrolling 55 patients. CVM stated it would be unlikely that we could concur with the proposal. CVM's regulations do not provide for orphan drug status or conditional approvals. Nor

do we have the legal authority to require additional studies after the initial approval. We need to gather both safety and effectiveness data from the field study. There should be enough dogs treated to provide inferential value.

Interim analysis was also discussed. CVM stated that it is not standard practice for us to allow interim analysis. However, the proposal may be included in the protocol for review.

**Target Animal Safety Studies (Nonclinical Studies):**

The sponsor has conducted multiple nonclinical studies in rats and dogs. A 28-day oral toxicity study was conducted in dogs by administering 0, 15, 50, and 150 mg/kg/day by gavage. It was concluded that the No Observable Adverse Effect Level (NOAEL) is 15 mg/kg. At 15 mg/kg/day, transient vomiting and diarrhea were noted. The NOAEL determination will be used to justify the starting dose in the field study.

Results from the 13-week oral toxicity study in dogs are pending. Dogs were dosed at 0, 4, 12, and 41 mg/kg/day by gavage.

The sponsor is currently conducting a 9-month oral toxicity study in dogs. Dogs were dosed at 0, 5, 15, and 50 mg/kg/day by gavage. CVM stated that this study is needed to obtain an open ended label to allow continual use of the drug. Typically a 6 month target animal safety study is necessary at 1, 3, and 5 times the recommended dosage. CVM stated the 1X dose is considered to be 20 mg/kg/day, the maximum dose administered in the field study. The purpose of administering multiples dosages of the drug is to define the toxic syndrome and therapeutic index. The studies conducted to date and this study may be acceptable to support the target animal safety technical section based upon the toxicities observed at dosages above 20 mg/kg/day. The sponsor is conducting the study for 9 months to support an IND in humans. CVM stated that a pharmacokinetic study is needed to bridge between the liquid formulation used in this study and the final market formulation.

The sponsor stated that the final market formulation will have four tablet sizes, 25, 50, 100, and 150 mg. CVM requested that the sponsor look at the dose range based upon body weight administered in the safety studies and discuss how this reflects upon safety for the field study. The smallest dogs may be receiving the largest dose per weight.

The sponsor provided a statistical justification for the number of animals used in the field study. CVM stated that while we look for statistical significance, it is important to have a sufficient number of cases to provide adequate inferential value about the use of the drug under actual conditions of use in the target population. It will be the first time the drug is used in dogs with mast cell tumors under the direction of multiple investigators. We also obtain additional information regarding the safety of the drug used in various breeds under actual conditions of use, with the owners dosing the dogs. To obtain this additional information, we ask that a minimum of 100 dogs be treated with the drug. The potential for drop outs and early withdrawals should be taken into consideration when determining

the number of animals to be enrolled in the study. The protocol should address the minimum and maximum number of animals enrolled at each site.

CVM stated that the safety data does not need to be submitted prior to conducting the field study. When the target animal safety is submitted, all raw data for the studies intended to support the technical section should be submitted along with any translations, if needed. Summaries of all other safety studies conducted in any species (e.g., human, rat or dog) should be submitted in the data package.

**Minor Use in a Major Species:**

The minor use guidance was discussed. The drug may qualify as a minor use in a major species. Currently, the guidance provides very little additional benefit. However, there is a new law before Congress. If the law passes, it could provide immediate benefits to the sponsor. Currently there is not a definition to determine what would qualify as a minor use in a major species. The sponsor could provide a proposal with scientific justification stating why the drug should be considered a minor use in the major species.

**Expedited Review Status:**

CVM stated that the drug would probably qualify for expedited review status (ERS). Expedited review status would reduce the review time for each submission and move it up higher in the reviewer's queue. Data submissions normally have a review time of 180 days. ERS reduces the review time to 90 days. The sponsor should submit a request for ERS with a scientific justification to support the request. Please see CVM's Policy and Procedure Manual Guide 1243.3120 on our website for additional information.

**Pharmacokinetic Data:**

The sponsor indicated that several pharmacokinetic studies were conducted, including a radiolabel study providing information on the mass balance and tissue distribution of this drug in dogs. They also noted that a bridging study has already begun comparing the oral solution used in the toxicology/target animal safety study versus the proposed final market formulation. That study employs a laboratory batch of the product at a strength their original write-up suggested would not be manufactured for marketing purposes. CVM indicated that executed bridging study employing a laboratory batch of the proposed product would not be acceptable.

Regarding their inquiry as to whether or not in vitro dissolution data can be used in lieu of submitting any in vivo bioequivalence study data, CVM indicated that this option would not be acceptable. Firstly, this product is poorly soluble (based upon traditional Biopharmaceutics Classification System specifications). Accordingly, this drug would be classified as either Class II (highly permeable, poorly soluble) or Class IV (poorly soluble, poorly permeable). If it is a Class II compound, in vitro/in vivo correlations need to be established before in vitro dissolution data can support in vivo bioequivalence. If it is a Class IV compound, this is considered a highly problematic drug and only in vivo bioequivalence studies would suffice. However, they were informed that when conducting the in vivo bridging (bioequivalence) study, in vitro dissolution data will be needed to support the waiver of the need to conduct studies on the other dosage strengths.

The dissolution method should be consistent with that agreed upon by the Division of Manufacturing Technologies (HFV-140).

The sponsor asked if the largest size tablet needs to be used in the in vivo bioequivalence trial. CVM explained that since veterinary medicine doses on a mg/kg basis, such a requirement would necessitate the use of giant breed animals. Such a requirement is not tenable under most study conditions, and therefore CVM asks only that the highest mg/kg dose is administered to medium size animals. In vivo bioequivalence study requirements for the additional tablet strengths are then waived if there is compositional proportionality to the strength tablets that underwent in vivo bioequivalence evaluation and if acceptable in vitro dissolution data are submitted. CVM also told the sponsor that all pivotal pharmacokinetic studies should be conducted with pilot batches (10% of full production scale batches), not laboratory batches. Accordingly, the pivotal bridging study should be conducted using the pilot batch that will undergo stability testing for the Chemistry, Manufacturing and Controls (CMC) portion of this application.

The sponsor was advised to submit a bridging study protocol, along with the proposed dissolution method and method of analysis (which we assume will be the f2 criterion). Since the bridging study is intended solely to cover safety, we are concerned with only the upper bound, not the lower bound. The lower bound pertains to effectiveness, which will be determined on the basis of clinical trials.

One concern expressed by CVM is the potential for food to increase the extent of drug absorption. The sponsor indicated that since the oral solution is ~85% bioavailable, they don't believe that this will be a problem. Nevertheless, the sponsor needs to provide information confirming that unexpectedly high drug concentrations will not occur if the product is administered in the prandial state. If they have data confirming that the drug is nearly 100% bioavailable as the oral solution under fasted condition, this should be provided to CVM to address this issue. In this regard, it should be noted that AB Science stated that rats tended to have more bone marrow effects than did dogs, and that they believe this to be attributable to the higher serum drug concentrations observed in rats.

A final point of concern pertained to dose bands and the exact dosages used in the safety study. The sponsor noted that the product will be coated to minimize owner exposure to the drug. CVM noted that this, by definition, prevents that the tablets be scored. The sponsor agreed to this point. With this in mind, the proposed tablet strengths will result in a wide range of mg/kg doses, depending upon the weight of the dog. AB Science indicated that they are considering the manufacture of an additional (25 mg) dosage strength. CVM recommended that AB Science provide information on the maximum dose within each of the tablet strengths (based upon weight ranges) and that this will be used to determine the adequacy of doses used in the toxicology/target animal safety study.

**CMC:**

Liver powder is added to the inside of the tablet in case a dog bites the tablet they will not be adverse to taking the pill again. The liver powder is not intended for advertising for palatability. The pills will be coated to protect the owners and won't be scored. The liver flavor is inside the pill, not in the coating.

**Phased Review of the INAD:**

Under the INAD, CVM provides for phased review of the technical sections necessary for approval of a new animal drug. The technical sections are:

- Effectiveness
- Target Animal Safety
- CMC
- Environmental Assessment
- Labeling
- Freedom of Information (FOI) Summary
- All Other Information

Each technical section is submitted separately for review. All data to support the technical section is submitted together. The wording for the labeling relevant to the technical section, as well as the component of the FOI Summary are submitted with each technical section. After all technical sections are complete, an Administrative NADA is filed to request approval.

A client information sheet may be included with the labeling. Various formats are acceptable including a question and answer format.

**U.S. Agent:**

Prior to submitting the Administrative NADA, the sponsor should identify a US Agent. All correspondence regarding the NADA will be directed to them. In the meantime, Anne-Virgine Eggimann and Emmanuelle Voisin are the company contacts for correspondence.

Lisa M. Troutman, MS, DVM  
Veterinary Medical Officer, HFV-112

cc: HFV199/INAD 11206 A0000  
LTroutman/HFV112/12-18-03  
Final: gsg/3-10-04  
cc: CVM Records\ONADE\I011206A0000met.min

# EXHIBIT I

## NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION

Form Approved: OMB No. 0910-0117  
Expiration Date: 03/31/05

**PAPERWORK REDUCTION ACT STATEMENT:** A Federal agency may not conduct or sponsor, and a person is not required to respond to, a collection of information, unless it displays a current valid OMB control Number. The public reporting burden for the collection of information is estimated to vary from 15 minutes to 2 hours, with an average of 30 minutes per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary information, and completing and reviewing the collection of information. Send comments regarding the burden estimate or any other aspect of this collection of information to the Food and Drug Administration, Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

**Submit this notice to:**

Food and Drug Administration  
Center for Veterinary Medicine  
Document Control Unit, HFV-199, Room N-403  
(Attention: Review Division HFV- )  
7500 Standish Place  
Rockville, Maryland 20855

DATE: Feb 1<sup>st</sup>, 2005

INAD / IFA NO: INAD 11206

STUDY / TRIAL ID: AB1010 PIIMCT 04003

DRUG SHIPMENT NO: 1

TYPE OF SHIPMENT:

☒ Initial

☐ Discontinued

☐ Supplement

☐ Other

The sponsor, AB Science 3 Avenue George V, 75008 Paris, France, submits a notice of claimed investigational exemption for the shipment or delivery of a new animal drug under the provisions of 21 CFR 311.1. This information is submitted in paper (in triplicate).

### I. Shipment ☒ or Receipt ☐ Information

1. NAME(S) OF THE DRUG(S)

Established name(s): AB 1010

Trade name(s):

2. PROPOSED USE OF THE DRUG(S): MAST CELL TUMOR TREATMENT

3. DATE OF DRUG SHIPMENT (OR RECEIPT): FEB 03, 2005

4. TOTAL QUANTITY (WT. OR VOL.) AND CONCENTRATION OF DRUG(S) SHIPPED (OR RECEIVED): 32 BOTTLES OF 50 TABLETS

Each tablet contains 25, 100 or 150 mg AB1010base or is the matching placebo

5. TYPE OF STUDY / TRIAL: DOUBLE-BLIND RANDOMIZED STUDY VS PLACEBO

6. INTENDED USE OF STUDY OR TRIAL:

☒ Pivotal (intended for support of NADA or ANADA)

☐ Non-pivotal

7. NAME AND ADDRESS OF INVESTIGATOR: DAVID ARGYLE

UNIVERSITY OF WISCONSIN, SCHOOL OF VETERINARY MEDICINE

2015 LINDEN DRIVE

MADISON WI 53703-1102

Phone Number: 608-262-5990

8. LOCATION OF STUDY / TRIAL:

UNIVERSITY OF WISCONSIN, SCHOOL OF VETERINARY MEDICINE

2015 LINDEN DRIVE

MADISON WI 53703-1102

9. NAME AND ADDRESS OF STUDY MONITOR: DIANE PROBASCO

Phone Number:

10. APPROXIMATE DATE OF STUDY / TRIAL

Start: February 2005

Finish: DECEMBER 2005

11. PROTOCOL SUBMITTED TO CVM:

☒ Yes

☐ No

If Yes, date submitted to CVM and/or CVM submission number: FEB 10, 2005

12. SPECIES OF ANIMALS: DOG

13. SIZE AND TYPE OF ANIMALS: ANY

14. APPROXIMATE NUMBER OF ANIMALS IN THIS STUDY/TRIAL:

Total: 125

Treated: 100

Control: 25

15. NUMBER OF ANIMALS PREVIOUSLY USED:

Total: 0

Treated:

Control:

16. MAXIMUM DAILY DOSE: 12.5 MG/KG

AND DURATION: 6 MONTHS

17. METHOD OF ADMINISTRATION: ORAL ROUTE

18. CONTRACT RESEARCH ORGANIZATIONS (CRO) USED:

☒ Yes

☐ No

Name and address of CRO: Harrison Clinical Research

Phone Number:

Description of obligations transferred to CRO: study monitoring

## II. Animals Intended For Human Food Purposes

1. DATE OF CVM AUTHORIZATION LETTER:

2. WITHDRAWAL PERIOD:

3. ACKNOWLEDGEMENT: Acknowledgment that the date and place of slaughter will be reported to FDA and Dr. Julie Cornett, USDA/FSIS, Technical Service Center, 1299 Farnam Street, Suite 300, Landmark Center, Omaha, NE, 68102, at least 10 days prior to shipment for slaughter. Experimentally treated animals will be identified to the inspector in charge of the slaughtering establishment when presented for antemortem inspection.

☐ Yes

☐ No

4. NOTIFICATION WAIVER: A waiver of requirements for notification of the date and place of slaughter after a 30-day holding and observation period following the required withdrawal period has been granted by FDA.

☐ Yes

☐ No

## III. Investigational New Animal Drug Labeling (Please select one label)

1. NEW ANIMAL DRUGS FOR TESTS *IN VITRO* AND IN LABORATORY RESEARCH ANIMALS:

☐ **Caution.** Contains a new animal drug for investigational use only in laboratory research animals or for tests *in vitro*. Not for use in humans.

2. NEW ANIMAL DRUGS FOR CLINICAL INVESTIGATION IN ANIMALS:

☒ **Caution.** Contains a new animal drug for use only in investigational animals in clinical trials. Not for use in humans. Edible products of investigational animals are not to be used for food unless authorization has been granted by the U.S. Food and Drug Administration or by the U.S. Department of Agriculture.

3. NEW ANIMAL DRUGS FOR EXPORT IN ANIMALS:

☐ **Caution.** Contains a new animal drug for use only in investigational clinical trials. Not for use in humans. Edible products from animals used for investigation are not to be used for food in any manner contrary to the requirements of the country in which the clinical trials are to be conducted.

If the drug is intended for food-producing animals, the label must also bear:

☐ No official withdrawal time has been established for this product under the proposed investigational use.

## IV. Sponsor Information

1. SPONSOR'S NAME: AB SCIENCE

2. SPONSOR'S ADDRESS: 3 AVENUE GEORGE V  
75008 PARIS  
FRANCE

3. SPONSOR CONTACT'S SIGNATURE:

4. SPONSOR CONTACT'S NAME: ALAIN MOUSSY

5. SPONSOR CONTACT'S PHONE NUMBER: +33 147 20 23 11

6. SPONSOR CONTACT'S FAX NUMBER: +33 147 20 24 11

7. SPONSOR CONTACT'S E-MAIL ADDRESS: ALAIN.MOUSSY@AB-SCIENCE.COM

## V. Comments

Are there additional comments?

~~Yes~~

No



INAD/IFA No.:

DATE:

**--NOTE: IF THE INVESTIGATION IS DISCONTINUED, THE CENTER FOR VETERINARY MEDICINE SHOULD BE NOTIFIED, GIVING THE REASON AND DISPOSITION OF THE DRUG.**

## EXHIBIT J

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 7,423,055

Docket No. 71247-0144

Issued: September 9, 2008

To: Ciufolini et al.

For: : 2-(3-AMINOARYL)AMINO-4-  
ARYLTHIAZOLES FOR  
THE TREATMENT OF DISEASES

Assignee: AB Science

APPOINTMENT OF SPECIAL POWER OF ATTORNEY

Commissioner for Patents  
Alexandria, VA 22313-1450

Sir:

AB SCIENCE, the undersigned assignee in the above-captioned patent, hereby appoints Conrad J. Clark (Reg. No. 30,340), and Christopher W. Brody (Reg. No. 33,613) as attorneys with full power to make an application for patent term extension for the above-captioned United States Patent No. 7,423,055 and to transact all business in the Patent and Trademark Office in connection with said application for patent term extension.

Please send all correspondence in connection with the patent term extension to:

Customer No. 22902  
CLARK & BRODY  
1700 Diagonal Road, Suite 510  
Alexandria, VA 22314  
Telephone: 202-835-1111  
Facsimile: 703-504-9415

Respectfully submitted,


Signature:

Printed Name:

Title:

Date:

Telephone No.

  
\_\_\_\_\_  
Alain Roussy  
\_\_\_\_\_  
CEO AB Science  
\_\_\_\_\_  
Jan 28<sup>th</sup> 2011  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**COPY**



**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**In re:** U.S. Patent No. 7,423,055 Attorney Docket No.: 71247-0144

**Issued:** September 9, 2008

**Inventors:** Ciufolini, et al.

**Assignee:** AB SCIENCE

**For:** 2-(3-Aminoaryl)Amino 4-Arylthiazoles For The Treatment Of Diseases

**MAIL STOP PATENT EXTENSION**

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

**APPLICATION FOR THE EXTENSION OF THE TERM  
OF THE UNITED STATES PATENT NO. 7,423,055  
UNDER 35 U.S.C. § 156**

Sir:

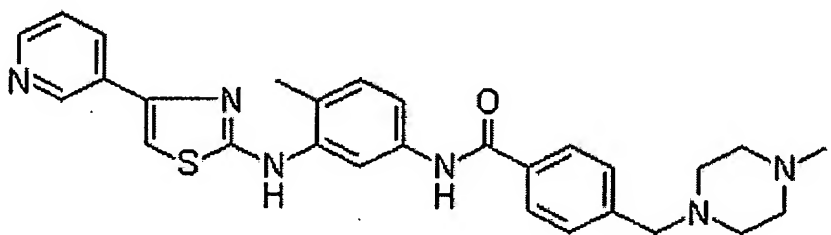
In accordance with 35 U.S.C. § 156 and 37 C.F.R. § 1.740, AB Science, a corporation of France, ("AB Science"), through the undersigned, represents that it is the owner of record of United States Patent No. 7,423,055 ("the '055 patent"), attached hereto as Exhibit A, and hereby requests an extension of the patent term thereof. A copy of the assignment and assignment recordation from the '055 patent, which were recorded on January 12, 2004 at Reel 014872, Frame 0028 confirming that all right, title, and interest resides in AB Science, is attached hereto as Exhibit B.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740. The sections of this application are numbered in a manner corresponding with

the numbering of subparagraphs (1) to (15) of 37 C.F.R. § 1.740(a) and follow the format set forth therein.

**(1) “A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.”**

The approved product is sold under the trade name KINAVET-CA1, the active ingredient of which is masinitib. A chemical name of masinitib is 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-4-yl-thiazol-2-ylamino)-phenyl]-benzamide, and the structure is shown below:



Synonyms for masinitib include AB1010, MM, and KINAVET. The molecular weight of masinitib is 498.67 g/mol, and its empirical formula is  $C_{28}H_{30}N_6OS$ . (See Product Label, Exhibit C, page 1).

As currently approved, the product sold under the trade name KINAVET-CA1 is indicated for the treatment of recurrent (post-surgery) or nonresectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and/or chemotherapy except corticosteroids in dogs. (See Product Label, Exhibit C, page 1). Currently, the approved product is available in the form of a tablet for oral administration. (See Product Label, Exhibit C, page 1).

**(2) “A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.”**

The product sold under the trade name KINAVET-CA1 (masinitib) was subject to regulatory review for an investigational new animal drug application (“INAD”) and a conditional

new animal drug application ("NADA") under section 571(b) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §§ 360ccc(b) ("FFDCA"). Section 571(b) authorizes the conditional approval of an application pending the full demonstration of effectiveness under section 512(d)(1)(E) (21 U.S.C. § 360b(d)(1)(E)) within 5 years. The Food and Drug Administration ("FDA") approved the KINAVET-CA1 product (conditional NADA 141-308) under the authority granted by section 571(b) of the FFDCA, 21 U.S.C. § 360ccc(b).

***(3) "An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred."***

The product sold under the trade name KINAVET-CA1 (masinitib) conditionally received permission for commercial marketing or use from the FDA pursuant to section 571(b) of the FFDCA, 21 U.S.C. § 360ccc(b), on December 15, 2010. According to the approval received from the FDA, the application is conditionally approved for one year from December 15, 2010 and is renewable annually for up to four additional one-year terms upon demonstration that Applicant is making sufficient progress toward meeting the approval requirements under section 512(d)(1)(E) of the FFDCA, the quantity of the drug distributed is consistent with the conditionally intended use, and the same drug in the same dosage form for the same intended use has not received approval under Section 512. Copies of the Product Label and FDA conditional approval letter are attached as Exhibits C and D, respectively.

***(4) "In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved."***

The active ingredient in the product sold under the trade name KINAVET-CA1 is masinitib. Masinitib has not been previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act or the Virus-Serum-Toxin Act.

***(5) "A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the last day on which the application could be submitted."***

This application is being submitted within the sixty days from receipt of the conditional approval under Section 571 of the FFDCa from the FDA. To the extent Section 571 of the FFDCa can serve as a basis for patent term extension, this application is being submitted within the sixty day period permitted for submission pursuant to 37 C.F.R. § 1.720(f), the last day for said submission being February 12, 2011.

***(6) "A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration."***

The complete identification of the patent for which extension is sought is as follows:

Inventors:	Marco Ciufolini, Camille Wermuth, Bruno Gielthen, and Alain Moussy
Patent No.:	7,423,055
Issue Date:	September 9, 2008
Expiration Date:	August 1, 2023

***(7) "A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings."***

A copy of U.S. Patent No. 7,423,055 ("the '055 patent"), for which this extension is sought, is attached hereto as Exhibit A.

***(8) "A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or re-examination certificate issued in the patent."***

A copy of the terminal disclaimer filed and received at the United States Patent and Trademark Office on April 10, 2008, which disclaims the terminal part of the '055 patent extending beyond the expiration of U.S. Patent Application No. 11/779,633, is attached hereto as Exhibit E.

No reexamination certificate for the '055 patent was issued.

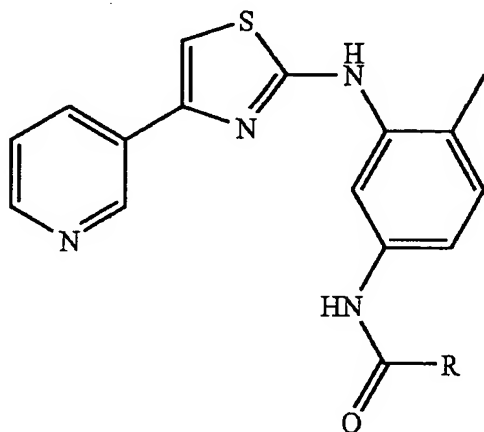
The first maintenance fee payment is not due until March 9, 2012 so no maintenance fee payment receipt is available.

***(9) "A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim"***

*and demonstrates the manner in which at least one such patent claim reads on: (i) The approved product, if the listed claims include any claim to the approved product; (ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and (iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product.”*

The '055 patent claims, *inter alia*, a composition of the approved product, *e.g.* the active ingredient of the product sold under the trade name KINAVET-CA1. More specifically, at least claims 1, 5, 7-10, 13-18, and 20 of the '055 patent read on the approved product. Claims 1, 5, 7-10, 13-18, and 20 are set forth below along with a showing as to how the claims read on the approved product:

**Claim 1.** A compound according to the following formula:



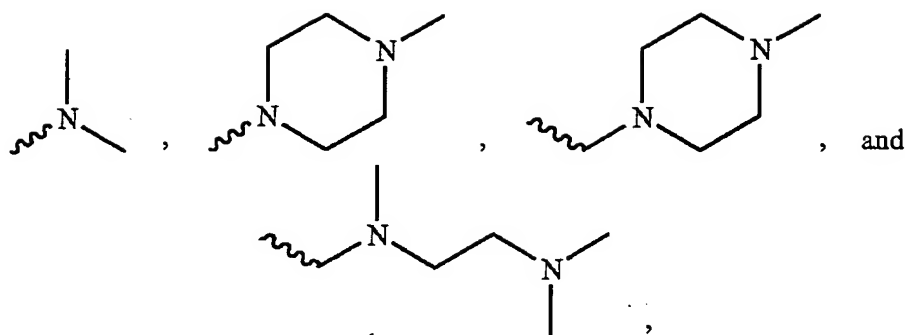
wherein R is:

H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality; or

a cycloalkyl, an aryl or heteroaryl group optionally substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

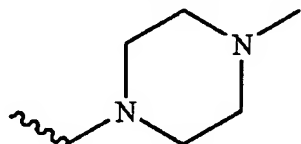
wherein said pendent basic nitrogen functionality is selected from the group consisting of





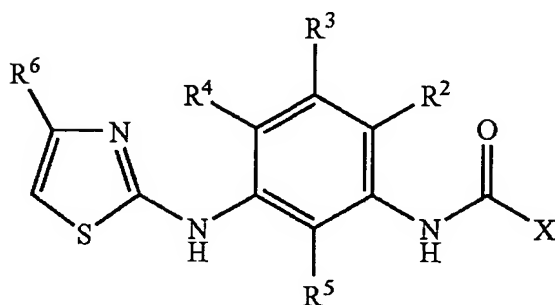
wherein the wavy line corresponds to the point of attachment.

Claim 1 reads on the approved product when  
R=aryl substituted by a pendant basic nitrogen functionality which is

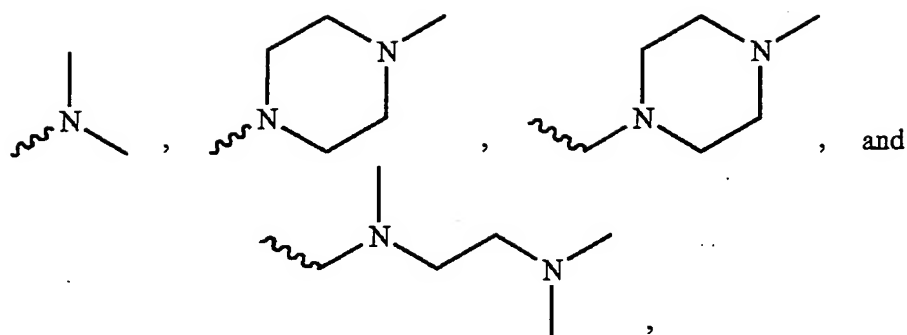


**Claim 5.** A compound according to formula II:

FORMULA II



wherein X is R or NRR' and wherein R and R' are independently chosen from H, an aryl, an heteroaryl, an alkyl and a cycloalkyl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;  
an aryl, an heteroaryl, an alkyl and a cycloalkyl group substituted with an aryl, an heteroaryl, an alkyl and a cycloalkyl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;  
wherein said pendant basic nitrogen functionality is selected from the group consisting of



wherein the wavy line corresponds to the point of attachment;

$R^2$  is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

$R^3$  is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

$R^4$  is halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

$R^5$  is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

$R^6$  is one of the following:

- (i) an aryl group optionally substituted by one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, or alkoxy;
- (ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear one or more substituents;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl, which may additionally bear one or more substituents.

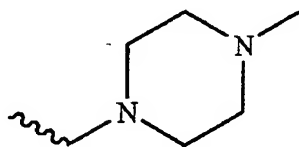
Claim 5 reads on the approved product when

$R^2, R^3, R^5$  = hydrogen

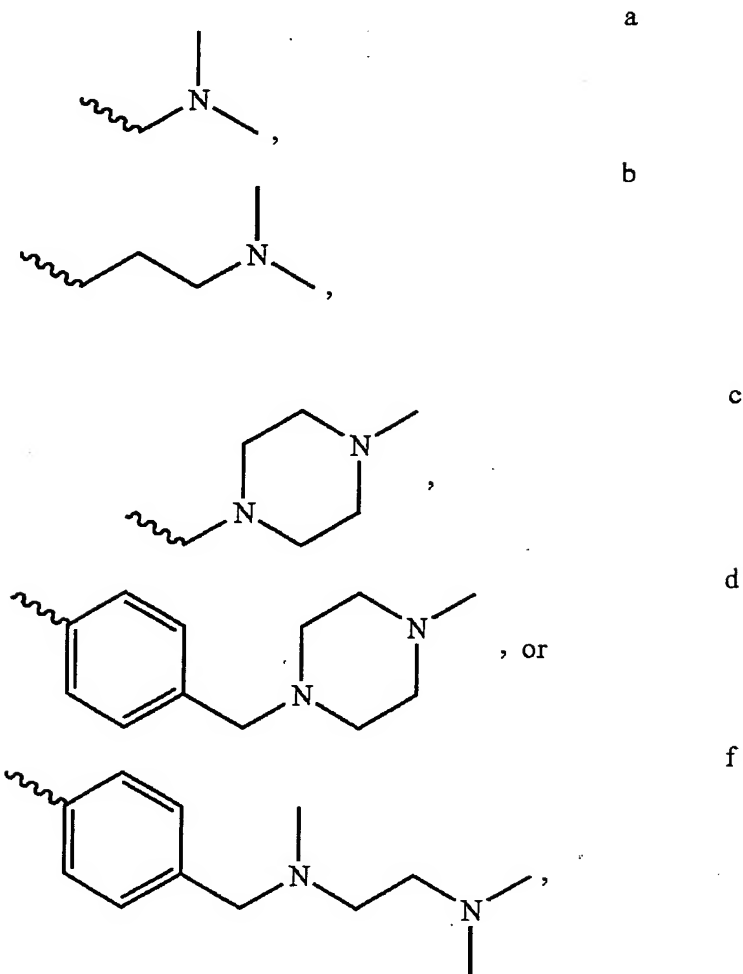
$R^4$  = methyl (alkyl with 1 carbon atom)

$R^6$  = 3-pyridyl group

X = R wherein R is aryl substituted by a pendant basic nitrogen functionality which is



**Claim 7.** A compound according to claim 5, wherein X is selected from the structures (a)-(d) and (f) shown below:



wherein the wavy line corresponds to the point of attachment to core structure of formula II.

Claim 7 reads on the approved product when

X= structure d),

$R^2, R^3, R^5$  = Hydrogen,

$R^4$  = methyl (alkyl with 1 carbon atom) and

$R^6$  = 3-pyridyl group.

**Claim 8.** A compound according to claim 7, wherein X is group (d) and  $R^6$  is a 3-pyridyl group.

Claim 8 reads on the approved product when

$R^2, R^3, R^5$  = hydrogen, and

$R^4$  = methyl (alkyl with 1 carbon atom).

**Claim 9.** A compound according to claim 7, wherein X is group (d) and  $R^4$  is a methyl group.

Claim 9 reads on the approved product when

$R^2, R^3, R^5$  = hydrogen, and

$R^6$  = 3-pyridyl group.

**Claim 10.** A compound according to claim 7, wherein X is group (d) and  $R^2$  and/or  $R^3$  and/or  $R^5$  is H.

Claim 10 reads on the approved product when

$R^2, R^3, R^5$  = hydrogen,

$R^4$  = methyl (alkyl with 1 carbon atom), and

$R^6$  = 3-pyridyl group.

**Claim 13.** The compound of claim S which is: 4-(4-methyl-piperazin-1-yl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 060) or 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-ylthiazol-2-ylamino)-phenyl]-benzamide (example 066).

Claim 13 reads on the approved product since it presents two alternative compounds, the latter one describing a chemical compound 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-4-yl-thiazol-2-ylamino)-phenyl]-benzamide, which encompasses the methanesulfonate-containing active ingredient of the approved product.

**Claim 14.** A compound which is: 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 066).

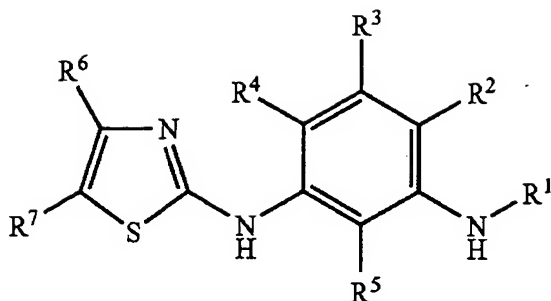
Claim 14 specifically claims the latter alternative of claim 13 and reads on the approved product for the same reason as set forth above for claim 13.

**Claim 15.** A composition comprising a compound of claim 14 and a pharmaceutically acceptable carrier.

Claim 15 reads on the approved product since the approved product, which is covered by claim 14, is in a pharmaceutically acceptable carrier.

**Claim 16.** A compound of formula I:

FORMULA I



wherein R<sup>1</sup> is: -C(O)R, -C(O)OR, or -CO-NRR', wherein R and R' are independently selected from the group consisting of hydrogen, aryl, heteroaryl, alkyl, and cycloalkyl, each optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality;

R<sup>2</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

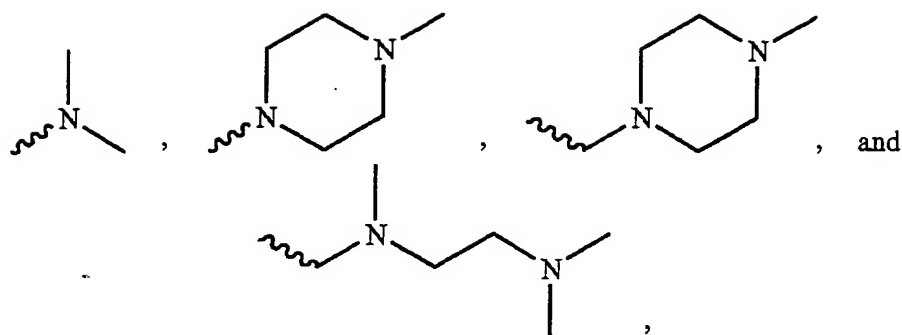
R<sup>3</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>4</sup> is halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>5</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>6</sup> is one of the following: (i) an aryl group such as phenyl optionally substituted by one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, or alkoxy; (ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear one or more substituents; or (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl, which may additionally bear one or more substituents;

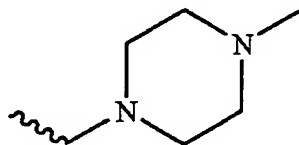
and R<sup>7</sup> is one of the following: (i) an aryl group such as phenyl optionally substituted by one or more substituents; (ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear one or more substituents; (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl, which may additionally bear one or more substituents; or (iv) H, a halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> and SO<sub>2</sub>-R'', wherein R'' is a linear or branched alkyl group optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality; wherein said pendant basic nitrogen functionality is selected from the group consisting of



wherein the wavy line corresponds to the point of attachment.

Claim 16 reads on the approved product when

$\text{R}^1 = -\text{C}(\text{O})\text{R}$  wherein R is aryl substituted by a pendant basic nitrogen functionality which is



$\text{R}^2, \text{R}^3, \text{R}^5 = \text{hydrogen},$

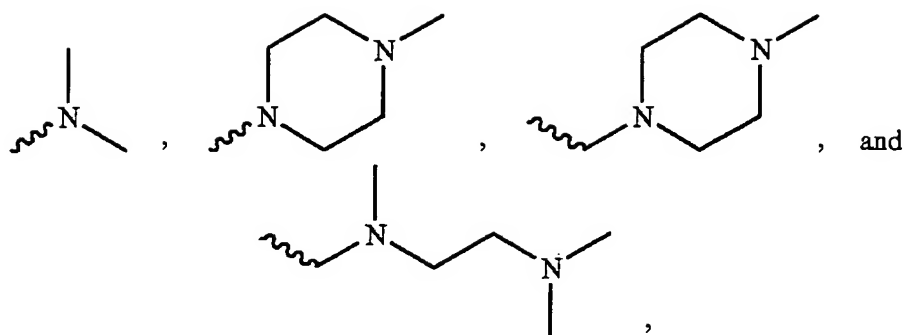
$\text{R}^4 = \text{methyl (alkyl with 1 carbon atom), and}$

$\text{R}^6 = \text{heteroaryl (3-pyridyl group)}.$

**Claim 17.** A composition comprising a compound of claim 16 in a pharmaceutically acceptable carrier.

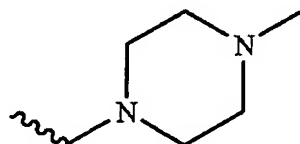
Claim 17 reads on the approved product since the approved product, which is covered by claim 16, is in a pharmaceutically acceptable carrier.

**Claim 18.** A compound according to claim 16, wherein  $\text{R}^1$  is  $\text{C}(\text{O})\text{R}$ , wherein R is independently selected from the group consisting of hydrogen, aryl, heteroaryl, alkyl, and cycloalkyl, each optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality; wherein said pendant basic nitrogen functionality is 60 selected from selected from the group consisting of



wherein the wavy line corresponds to the point of attachment.

Claim 18 reads on the approved product when  
 $\text{R1}$  (not  $\text{R}'$ ) is  $-\text{C}(\text{O})\text{R}$  wherein  $\text{R}$  is aryl substituted by a pendant basic nitrogen functionality which is



**Claim 20.** A pharmaceutical composition comprising a compound according to claim 18 and a pharmaceutically acceptable carrier.

Claim 20 reads on the approved product since the approved product, which is covered by claim 18, is in a pharmaceutically acceptable carrier.

***(10) “A statement, beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:***

***...(ii) For a patent claiming a new animal drug:***

***(A) The date a major health or environmental test on the drug was initiated, and any available substantiation of that date, or the date of an exemption under subsection (j) of Section 512 of the Federal Food, Drug, and Cosmetic Act became effective for such animal drug;***

***(B) The date on which a new animal drug application (NADA) was initially submitted and the NADA number; and***

***(C) The date on which the NADA was approved”.***

The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period for the product sold under the trade name KINAVET-CA1 are as follows:

(a) A letter dated March 11, 2004 from the FDA administratively assigned Investigational new animal drug (“INAD”) application number 011206. (Attached as Exhibit H). A Notice of Claimed Investigational Exemption (NCIE) for a New Animal Drug was filed with the FDA on February 1, 2005. (Attached as Exhibit I). In addition, studies relevant to the conditional approval for the product sold under the trade name KINAVET-CA1 were conducted as early as April 2003, e.g., 4-Week Toxicity Study described in Section III, B of the Freedom of Information Summary attached in Exhibit G. Accordingly, Applicant believes that the date a major health or environmental test on the drug was initiated or the date of an exemption under subsection (j) of section 512 of the FFDCA is at least on or around February 1, 2005, if not earlier.

Although Applicant may be entitled to an earlier date under 37 C.F.R. § 1.740(a)(10)(ii)(A), for the purposes of calculating the patent term extension of the ‘055 patent based on the conditional approval of conditional NADA application 141-307 under Section 571(b) herein, Applicant will use February 1, 2005. Applicant notes that this date is well before September 9, 2008, the issue date of the ‘055 patent, and that 37 C.F.R. §1.778(d)(1)(i) requires subtraction from the patent term extension calculations the number of days on and before the date the patent issued. (b) The conditional new animal drug application under Section 571 was submitted on July 9, 2010 for conditional approval, and was assigned conditional NADA



number 141-308.

(c) Conditional NADA number 141-308 was conditionally approved by the FDA on December 15, 2010 (Exhibit D).

(d) According to the approval letter received from the FDA, the conditional application is conditionally approved for one year, which will expire on December 15, 2011. However, the conditional application is renewable annually for up to four additional one-year terms upon filing a request to renew this application within 90 days from the end of the one-year period demonstrating that Applicant is making sufficient progress toward meeting the approval requirements under section 512(d)(1)(E) of the FFDCa, the quantity of the drug distributed is consistent with the conditionally intended use, and the same drug in the same dosage form for the same intended use has not received approval under Section 512.

***(11) "A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities."***

A chronology of selected regulatory activities is attached hereto as Exhibit F to briefly describe certain activities undertaken with respect to the approval of the product under the trade name KINAVET-CA1 during the applicable regulatory review period and the dates applicable to such activities. Also attached as Exhibit G is the Freedom of Information Summary, which details the various tests conducted in connection with the regulatory review period.

*(12) "A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined."*

Applicant respectfully submits that 35 U.S.C. § 156 and the associated regulations do not clearly address whether a product reviewed under Section 571 of the FFDCA would be eligible for patent term extension. Applicant is unaware of any prior decisions by the USPTO or the FDA addressing this particular issue and believes that this is one of first impression for these regulatory agencies. Pursuant to § 156(d)(1), a patent term application "may only be submitted within the sixty-day period beginning on the date the product received permission under the provision of law under which the applicable regulatory review period occurred for commercial marketing or use." Therefore, Applicant submits this application within 60 days of receiving the FDA's conditional approval of KINAVET-CA1 (conditional NADA 141-308) to request administrative review whether conditional approval of an animal drug under Section 571 of the FFDCA can serve as a basis for patent term extension. If so, Applicant respectfully requests for an extension of **493 days**, the calculation of which is further described below. Should the delays based on regulatory review under Section 571 not be eligible for patent term extension under 35 U.S.C. § 156(g), then Applicant respectfully submits that a subsequent regulatory approval of KINAVET-CA1 under Section 512(b) should be considered as "the first permitted commercial marketing or use of the product" as required by § 156(a)(5)(A) and reserves the right to file a subsequent patent term extension application based on subsequent express approval under Section 512(b).

The conditional NADA application under Section 571(a) of the FFDCA is an alternative regulatory process to authorize the distribution and commercial marketing of new animal drugs "intended for a minor use or a minor species," instead of the so-called "traditional" NADA under Section 512 of the FFDCA. Pursuant to the statute, conditional NADA applications under Section 571(a) "must comply in all respects with the provisions of section 512 of this Act" except for certain statutorily exempt sections. In particular, the statute states that "[n]ew animal drugs are subject to application of the same safety standards that would be applied to such drugs under section 512(d) (including, for antimicrobial new animal drugs, with respect to antimicrobial resistance)." 21 U.S.C. §360ccc(a)(1). Consistent with the language of the statute, and the FDA's guidelines regarding minor use and minor species animal drug applications, the

conditional approval issued under section 571(b) of the Federal Food, Drug, and Cosmetic “provides for animal drug marketing after all safety and manufacturing components of a new animal drug approval have met the standards of section 512 of the act (for the effectiveness component, a reasonable expectation of effectiveness must be established, after which sponsors have up to 5 years to complete the demonstration of effectiveness by the standards of section 512 of the act and achieve a full approval).” 70 Fed. Reg. 56394 (Sept. 27, 2005).

In addition to incorporating the substantive requirements of Section 512 of the FFDCA, the regulatory approval process under Section 571 is closely integrated with the statutory process under Section 512. Most notably, Section 512(b)(3) specifically incorporates a process for “[a]ny person intending to file an application under paragraph (1), section 571” to obtain one or more conferences with the FDA prior to submission of the conditional NADA. Applicant also notes that Section 512 refers to a conditional approval of an application filed pursuant to Section 571 as one possible route for an animal drug to be reviewed and deemed safe by the FDA. See 21 USC § 360b(a)(1)(B) and (a)(2)(A)(ii). Section 512(f), (g), (i), (l)(1) and (p)(1) provide identical review and record keeping processes for both Section 512 and Section 571 applications including: process for addressing decisions refusing, withdrawing or suspending approval; process for granting an order; process for publication in the Federal Register; requirements for record keeping and requirements for public access to safety and effective data.

In light of the integrated approval provisions of Sections 512 and 571 and the specific procedure established in Section 512(b) for initiating Section 571 applications, Applicant respectfully submits that the statutory language does not clearly address whether a product reviewed under Section 571 of the FFDCA would be eligible for patent term extension. Should Section 571 of the FFDCA be construed to be part of a regulatory regime that is eligible for patent term extension under 35 U.S.C. §156(g) (for example, as a type of Section 512(b) application), Applicant believes it appropriate to refer to the dates of submission and approval of NADA 141-308 below.

To the extent Section 571 of the FFDCA can serve as a basis for patent term extension, Applicant respectfully submits that that the '055 patent should be eligible for an extension and estimates the extension to be **493 days**, the calculation of which is described below. Applicant

notes that the calculations provided below reflect the conditional approval of conditional NADA 141-308 on December 15, 2010. Should the delays based on regulatory review under Section 571 not be eligible for patent term extension under 35 U.S.C. §156(g), Applicants respectfully submit that the calculations provided in Sections A, B and C are not applicable and reserve the right to submit alternative calculations based on a subsequent Section 512(b) regulatory approval.

A. Eligibility:

(a) Pursuant to 35 U.S.C. § 156(a), the '055 patent claims a composition of the active ingredient;

(b) Pursuant to 35 U.S.C. § 156(a)(1), the term of the '055 patent has not expired before submission of this application for extension;

(c) Pursuant to 35 U.S.C. § 156(a)(2), the term of the '055 patent has never been extended;

(d) Pursuant to 35 U.S.C. § 156(a)(3), the application for extension is submitted by the owners of record of the '055 patent;

(e) To the extent Section 571 of the FFDCA can serve as a basis for patent term extension, Applicant respectfully submits that the approved product, sold under the trade name KINAVET-CA1, has been subject to a regulatory review period before its commercial marketing or use pursuant to 35 U.S.C. § 156(a)(4);

(f) To the extent Section 571 of the FFDCA can serve as a basis for patent term extension, Applicant respectfully submits that the permission for the commercial marketing or use of the product sold under the trade name KINAVET-CA1 after the regulatory review period is the first permitted commercial marketing or use of this product pursuant to 35 U.S.C. § 156(a)(5).

(g) Pursuant to 35 U.S.C. § 156(c)(4), no other patent has been extended for the same regulatory review period for the approved product sold under the trade name

KINAVET-CA1.

B. Regulatory Review Period:

(a) The period from **February 1, 2005** (as discussed above, the date a major health or environmental test on the drug was initiated or the date of an exemption under subsection (j) of section 512 of the FFDCA is at least on or around February 1, 2005, if not earlier) to July 9, 2010 (the date the conditional NADA under Section 571 was initially submitted) is 1984 days. To the extent Section 571 of the FFDCA can serve as a basis for patent term extension, Applicant respectfully submits that the “Testing Phase” should be 1984 days pursuant to 37 C.F.R. § 1.778(c)(1).

(b) Pursuant to 37 C.F.R. § 1.778(c)(2), the period from July 9, 2010 (the date the conditional NADA under Section 571 was initially submitted) to December 15, 2010 (the date of NADA conditional approval) is 159 days. To the extent Section 571 of the FFDCA can serve as a basis for patent term extension, Applicant respectfully submits that the “Approval Phase” should be 159 days pursuant to 37 C.F.R. § 1.778(c)(2).

C. Extended Patent Term:

(a) The number of days in the regulatory review period described in section B above which were on and before September 9, 2008, the date on which the '055 patent issued, is 1316 days. Accordingly, 1316 days are subtracted from the regulatory review pursuant to 37 C.F.R. § 1.778(d)(1)(i).

(b) As demonstrated in Exhibit F, the Applicant acted with due diligence during the regulatory review period. Accordingly, zero (0) days are subtracted from the regulatory review period pursuant to 37 C.F.R. § 1.778(d)(1)(ii).

(c) To the extent Section 571 of the FFDCA can serve as a basis for patent term extension, one half of the number of days remaining in the Testing Phase (as calculated in Section B above) after the consideration of potential reductions pursuant to paragraphs (a) and (b) above is 334 days. Accordingly, 334 days are subtracted from the regulatory review period

pursuant to 37 C.F.R. § 1.778(d)(1)(iii). Applicants respectfully submit that after the above adjustments, the total remaining Testing Phase and Approval Phase is 493 days (334 days plus 159 days), should the delays based on regulatory review under Section 571 be eligible for patent term extension under 35 U.S.C. § 156(g).

(d) The period remaining in the term of the patent (set to expire August 1, 2023) measured from the date of conditional approval of the product sold under the trade name KINAVET-CA1 (December 15, 2010) (4612 days) when added to the period of extension (493 days) is 5105 days, which is less than fourteen (14) years. Accordingly, the fourteen (14) year limitation set forth in 37 C.F.R. § 1.775(d)(2)-(4) does not operate to reduce the regulatory review period.

(e) The period of extension (493 days) is less than five (5) years. Accordingly, the five (5) year limitation set forth in 37 C.F.R. § 1.778(d)(5)(i)(ii) does not operate to further reduce the regulatory review period.

***(13) "A statement that applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to any determination of entitlement to the extension sought."***

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought pursuant to 37 C.F.R. § 1.765.

As discussed above, Applicants respectfully submits that 35 U.S.C. § 156 and the associated regulations do not clearly address whether a product conditionally approved under Section 571 of the FFDCA would be eligible for patent term extension. Applicant is unaware of any prior decisions by the USPTO or the FDA addressing this particular issue and believes that this is one of first impression by for these regulatory agencies. Therefore, Applicant submits this application to request administrative determination of whether conditional approval of an animal drug under Section 571 of the FFDCA can serve as a basis for patent term extension.

***(14) "The prescribed fee for receiving and acting upon the application for extension."***

The prescribed fee for receiving and acting upon this application is believed to be \$1,120.00 pursuant to 37 C.F.R. § 1.20(j)(1). A fee transmittal letter is attached to pay the application fee. The Commissioner is authorized to charge this fee and any additional required fees, or credit any overpayment, to Deposit Account No. 50-1088.

***(15) "The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed."***

Please direct all inquiries and correspondence relating to this application to:

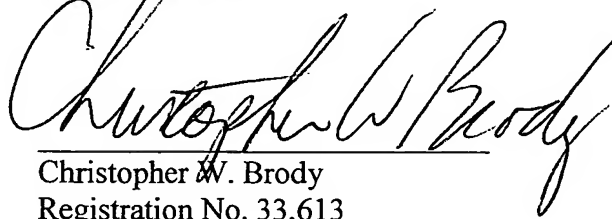
Christopher W. Brody  
Clark & Brody  
1700 Diagonal Road, Suite 510  
Alexandria, VA 22314  
Tel:(202)835-1753  
Fax (703) 504-9415

A power of attorney (Exhibit J) is also enclosed so that the record will reflect correspondence should be addressed to Customer No. 22902.

***(16) "The application under this section must be accompanied by two additional copies of such application (for a total of three copies)."***

This Application is accompanied by two additional copies of such application for a total of three copies as required by 37 C.F.R. § 1.740(b). The undersigned attorney for Applicants hereby states that these copies are accurate and true duplicates of the original.

Respectfully submitted,  
CLARK & BRODY



Christopher W. Brody  
Registration No. 33,613

***Customer No. 22902***

1700 Diagonal Road, Suite 510  
Alexandria, VA 22314  
Telephone: 202-835-1111  
Facsimile: 703-504-9415  
Docket No.: 71247-0144  
Date: February 11, 2011



**PROPRIETARY MATERIAL NOT OPEN TO PUBLIC**  
**DO NOT SCAN**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**In re:** U.S. Patent No. 7,423,055 Attorney Docket No.: 71247-0144  
**Issued:** September 9, 2008  
**Inventors:** Ciufolini, et al.  
**Assignee:** AB SCIENCE  
**For:** 2-(3-Aminoaryl)Amino 4-Arylthiazoles For The Treatment Of Diseases

**MAIL STOP PATENT EXTENSION**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**FEE TRANSMITTAL LETTER**  
**FOR AN APPLICATION FOR EXTENSION UNDER 35 U.S.C. § 156**

Sir:

Transmitted herewith is an Application for Extension of Patent Term Under 35 U.S.C. § 156 for U.S. Patent No. 7,423,055 accompanied by two additional copies. The undersigned attorney for Applicants hereby state that these copies are certified to be duplicates of the original. Each copy contains the following exhibits:

Exhibit A	U.S. Patent No. 7,423,055
Exhibit B	Assignment Recordation & Assignment
Exhibit C	Approved Product Labels
Exhibit D	FDA Approval Letter
Exhibit E	Terminal Disclaimer
Exhibit F	Compendium of Certain Regulatory Activities in connection with the product sold under the trade name KINAVET-CA1 INAD and NADA (Marked as <b>PROPRIETARY MATERIAL NOT OPEN TO PUBLIC</b> in accordance with MPEP §§2760 and 724.02)
Exhibit G	Freedom of Information Summary for KINAVET-CA1
Exhibit H	Letter dated March 11, 2004 from the FDA administratively assigning INAD No. 011206
Exhibit I	Notice of Claimed Investigational Exemption (NCIE) for a New Animal Drug filed with the FDA on February 1, 2005

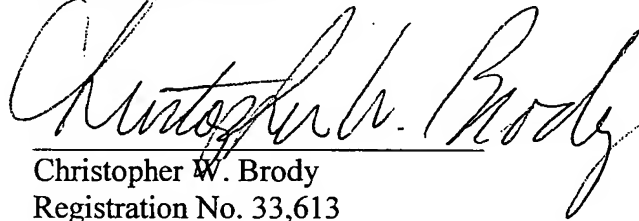
**PROPRIETARY MATERIAL NOT OPEN TO PUBLIC**  
**DO NOT SCAN**

Exhibit J      Power of Attorney

Applicant respectfully request that the Exhibit F provided herewith be treated as PROPRIETARY information and not be made public as part of the patent file in accordance with MPEP §2760.

Please charge Deposit Account No. 50-1088 the fee of \$1,120.00 for the application fee. The Director is hereby authorized to charge any additional fees, which may be required, or credit any overpayment to Deposit Account No. 50-1088.

Respectfully submitted,  
CLARK & BRODY



Christopher W. Brody  
Registration No. 33,613

***Customer No. 22902***

1700 Diagonal Road, Suite 510  
Alexandria, VA 22314  
Telephone: 202-835-1111  
Facsimile: 703-504-9415  
Docket No.: 71247-0144  
Date: February 11, 2011

# EXHIBIT A



US007423055B2

(12) **United States Patent**  
**Ciufolini et al.**

(10) **Patent No.:** **US 7,423,055 B2**  
 (45) **Date of Patent:** **\*Sep. 9, 2008**

(54) **2-(3-AMINOARYL)AMINO-4-ARYL-THIAZOLES  
 FOR THE TREATMENT OF DISEASES**

(75) Inventors: **Marco Ciufolini, Lyons (FR); Camille  
 Wermuth, Strasbourg (FR); Bruno  
 Gielthen, Illkirch (FR); Alain Moussy,  
 Paris (FR)**

(73) Assignee: **AB Science, Paris (FR)**

(\*) Notice: Subject to any disclaimer, the term of this  
 patent is extended or adjusted under 35  
 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-  
 claimer.

(21) Appl. No.: **10/632,101**

(22) Filed: **Aug. 1, 2003**

(65) **Prior Publication Data**

US 2004/0110810 A1 Jun. 10, 2004

**Related U.S. Application Data**

(60) Provisional application No. 60/400,064, filed on Aug.  
 2, 2002.

(51) **Int. Cl.**

**A61K 31/44** (2006.01)

**C07D 417/04** (2006.01)

**C07D 417/14** (2006.01)

(52) **U.S. Cl.** ..... **514/342; 514/370; 546/270.4;**  
**548/194; 544/364**

(58) **Field of Classification Search** ..... **548/190,**  
**548/194; 546/270.4; 514/342, 370**  
 See application file for complete search history.

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

3,192,225 A 6/1965 Spivack et al.

3,201,409 A \* 8/1965 Dexter et al. .... 548/193  
 3,467,666 A \* 9/1969 Dexter et al. .... 548/193  
 5,521,184 A 5/1996 Zimmermann  
 6,291,514 B1 \* 9/2001 Illig et al. .... 514/447  
 2001/0044545 A1 \* 11/2001 Dhanoa et al. .... 548/190  
 2003/0158199 A1 \* 8/2003 Stieber et al. .... 514/242

#### FOREIGN PATENT DOCUMENTS

WO WO-96/01825 A1 \* 1/1996  
 WO WO 99/03854 A 1/1999  
 WO WO 00/33842 A 5/2000  
 WO WO 00/75120 A 12/2000  
 WO WO 01/64200 A 9/2001  
 WO WO 01/64674 A 9/2001  
 WO WO 02/080925 A 10/2002  
 WO WO 03/062215 A 7/2003

#### OTHER PUBLICATIONS

Golub et al., Science, vol. 286, Oct. 15, 1999, pp. 531-537.\*  
 Schantl et al., Synthetic Communications (1998), 28(8), pp. 1451-  
 1462.\*

\* cited by examiner

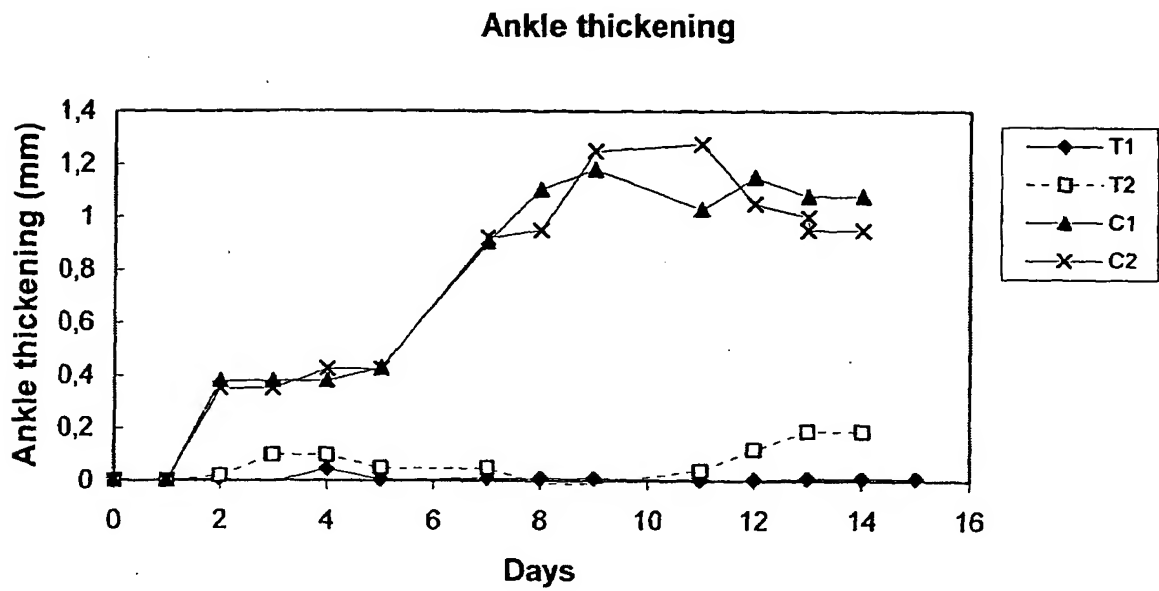
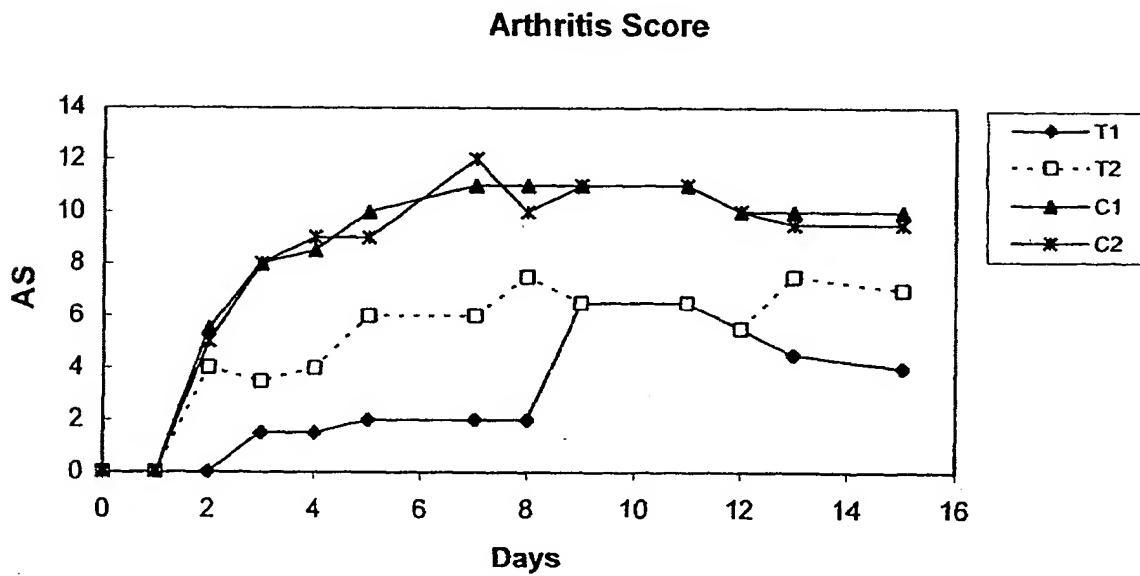
*Primary Examiner*—Laura L. Stockton

(74) *Attorney, Agent, or Firm*—Foley & Lardner

(57) **ABSTRACT**

The present invention relates to novel compounds selected  
 from 2-(3-aminoaryl)amino-4-aryl-thiazoles that selectively  
 modulate, regulate, and/or inhibit signal transduction medi-  
 ated by certain native and/or mutant tyrosine kinases impli-  
 cated in a variety of human and animal diseases such as cell  
 proliferative, metabolic, allergic, and degenerative disorders.  
 More particularly, these compounds are potent and selective  
 c-kit inhibitors.

**30 Claims, 2 Drawing Sheets**

**FIGURE 1****FIGURE 2**

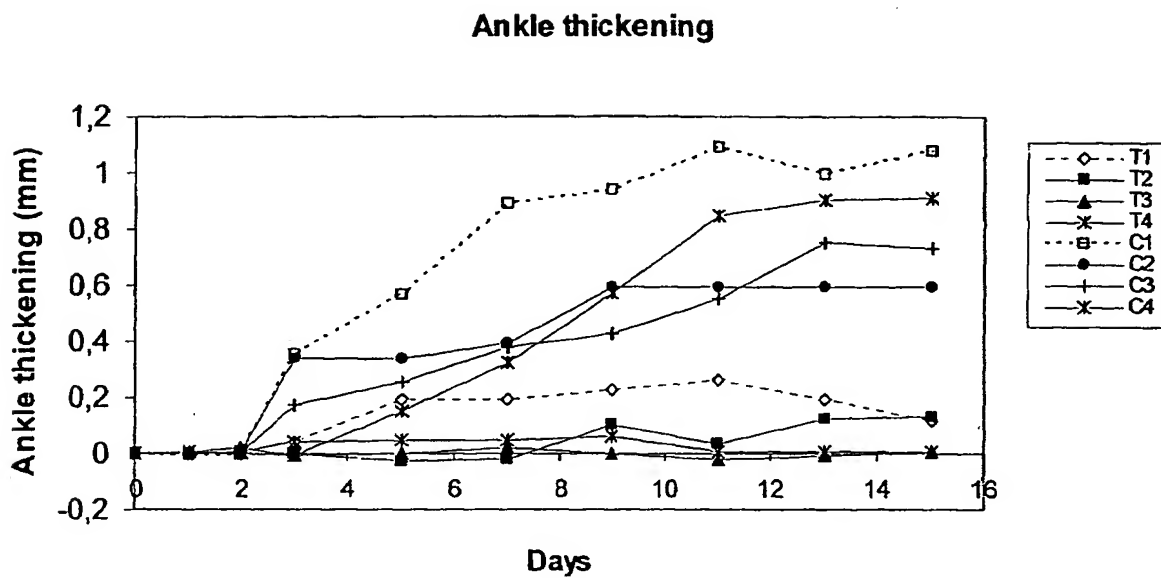


FIGURE 3

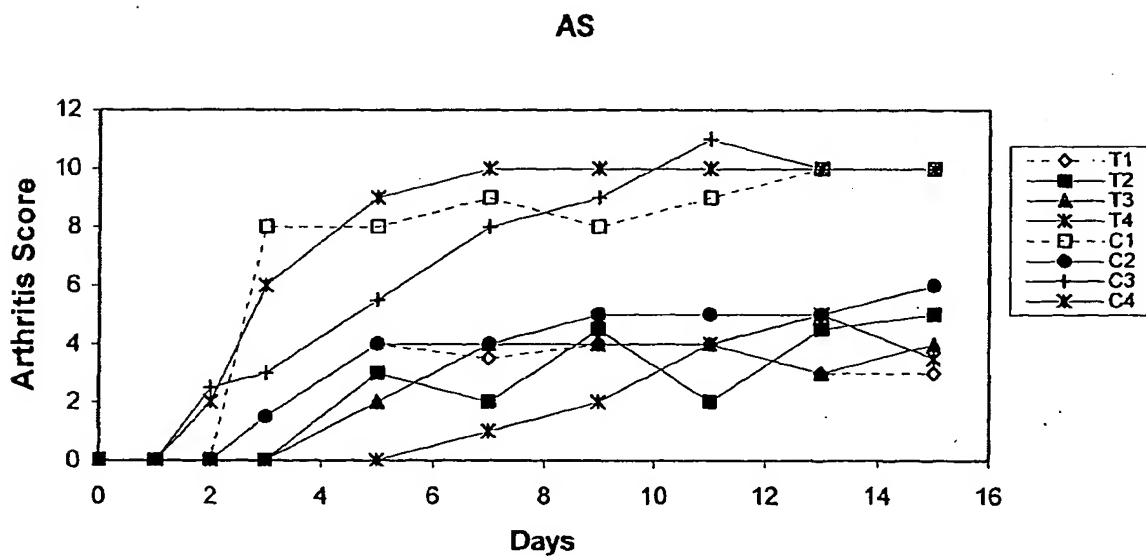


FIGURE 4

1

## 2-(3-AMINOARYL)AMINO-4-ARYL-THIAZOLES FOR THE TREATMENT OF DISEASES

### BACKGROUND OF THE INVENTION

The present invention relates to novel compounds selected from 2-(3-aminoaryl)amino-4-aryl-thiazoles that selectively modulate, regulate, and/or inhibit signal transduction mediated by certain native and/or mutant tyrosine kinases implicated in a variety of human and animal diseases such as cell proliferative, metabolic, allergic, and degenerative disorders. More particularly, these compounds are potent and selective c-kit inhibitors.

Tyrosine kinases are receptor type or non-receptor type proteins, which transfer the terminal phosphate of ATP to tyrosine residues of proteins thereby activating or inactivating signal transduction pathways. These proteins are known to be involved in many cellular mechanisms, which in case of disruption, lead to disorders such as abnormal cell proliferation and migration as well as inflammation.

As of today, there are about 58 known receptor tyrosine kinases. Other tyrosine kinases are the well-known VEGF receptors (Kim et al., Nature 362, pp. 841-844, 1993), PDGF receptors, c-kit and the FLK family. These receptors can transmit signals to other tyrosine kinases including Src, Raf, Frk, Btk, Csk, Abl, Fes/Fps, Fak, Jak, Ack, etc.

Among tyrosine kinase receptors, c-kit is of special interest. Indeed, c-kit is a key receptor activating mast cells, which have proved to be directly or indirectly implicated in numerous pathologies for which the Applicant filed WO 03/004007, WO 03/004006, WO 03/003006, WO 03/003004, WO 03/002114, WO 03/002109, WO 03/002108, WO 03/002107, WO 03/002106, WO 03/002105, WO 03/039550, WO 03/035050, WO 03/035049, U.S. 60/359,652 and U.S. 60/359,651.

It was found that mast cells present in tissues of patients are implicated in or contribute to the genesis of diseases such as autoimmune diseases (rheumatoid arthritis, inflammatory bowel diseases (IBD)) allergic diseases, tumor angiogenesis, inflammatory diseases, and interstitial cystitis. In these diseases, it has been shown that mast cells participate in the destruction of tissues by releasing a cocktail of different proteases and mediators such as histamine, neutral proteases, lipid-derived mediators (prostaglandins, thromboxanes and leucotrienes), and various cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, TNF- $\alpha$ , GM-CSF, MIP-1a, MIP-1b, MIP-2 and IFN- $\gamma$ ).

The c-kit receptor also can be constitutively activated by mutations leading to abnormal cell proliferation and development of diseases such as mastocytosis and various cancers.

For this reason, it has been proposed to target c-kit to deplete the mast cells responsible for these disorders.

The main objective underlying the present invention is therefore to find potent and selective compounds capable of inhibiting wild type and/or mutated c-kit.

Many different compounds have been described as tyrosine kinase inhibitors, for example, bis monocyclic, bicyclic or heterocyclic aryl compounds (WO 92/20642), vinylene-azaindole derivatives (WO 94/14808) and 1-cyclopropyl-4-pyridyl-quinolones (U.S. Pat. No. 5,330,992), styryl compounds (U.S. Pat. No. 5,217,999), styryl-substituted pyridyl compounds (U.S. Pat. No. 5,302,606), seleninols and selenides (WO 94/03427), tricyclic polyhydroxylic compounds (WO 92/21660) and benzylphosphonic acid compounds (WO 91/15495), pyrimidine derivatives (U.S. Pat. No. 5,521,184 and WO 99/03854), indolinone derivatives and pyrrole-substituted indolinones (U.S. Pat. No.

2

5,792,783, EP 934 931, U.S. Pat. No. 5,834,504, U.S. Pat. No. 5,883,116, U.S. Pat. No. 5,883,113, U.S. Pat. No. 5,886,020, WO 96/40116 and WO 00/38519), as well as bis monocyclic, bicyclic aryl and heteroaryl compounds (EP 584 222, U.S. Pat. No. 5,656,643 and WO 92/20642), quinazoline derivatives (EP 602 851, EP 520 722, U.S. Pat. No. 3,772,295 and U.S. Pat. No. 4,343,940) and aryl and heteroaryl quinazoline (U.S. Pat. No. 5,721,237, U.S. Pat. No. 5,714,493, U.S. Pat. No. 5,710,158 and WO 95/15758).

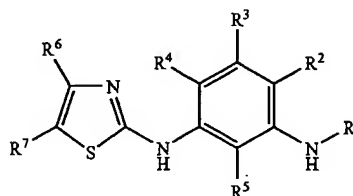
However, none of these compounds have been described as potent and selective inhibitors of c-kit or of the c-kit pathway.

In connection with the present invention, we have found that compounds corresponding to the 2-(3-aminoaryl)amino-4-aryl-thiazoles are potent and selective inhibitors of c-kit or c-kit pathway. These compounds are good candidates for treating diseases such as autoimmune diseases, inflammatory diseases, cancer and mastocytosis.

### BRIEF SUMMARY OF THE INVENTION

Therefore, the present invention relates to compounds belonging to the 2-(3-aminoaryl)amino-4-aryl-thiazoles. These compounds are capable of selectively inhibiting signal transduction involving the tyrosine phosphokinase c-kit and mutant forms thereof. In a first embodiment, the invention is aimed at compounds of formula I, which may represent either free base forms of the substances or pharmaceutically acceptable salts thereof:

FORMULA I



and wherein R<sup>1</sup> is:

- a) a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;
  - b) an aryl or heteroaryl group optionally substituted by an alkyl or aryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;
  - c) a —CO—NH—R, —CO—R, —CO—OR or a —CO—NRR' group, wherein R and R' are independently chosen from H or an aryl, heteroaryl, alkyl and cycloalkyl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;
- R<sup>2</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;
- R<sup>3</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;
- R<sup>4</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;
- R<sup>5</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

3

R<sup>6</sup> is one of the following:

- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy,

- iv) H, a halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>—R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; and R<sup>7</sup> is one of the following:

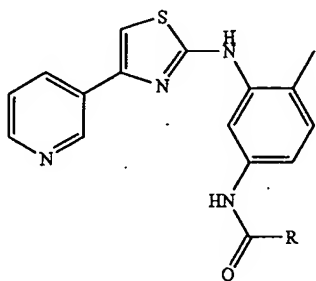
- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.

- iv) H, a halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>—R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

#### DETAILED DESCRIPTION OF INVENTION

The present invention provides compounds belonging to the 2-(3-(amino)aryl)amino-4-aryl-thiazoles, such as those described above with reference to Formula I. These compounds are capable of selectively inhibiting signal transduction involving the tyrosine phosphokinase c-kit and mutant forms thereof.

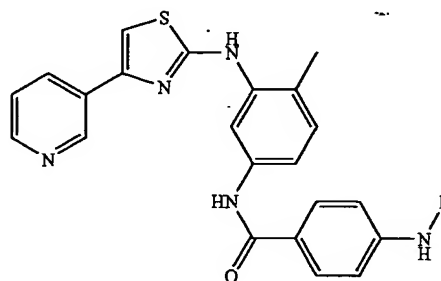
In another preferred embodiment, when R<sup>1</sup> has the meaning depicted in c) above, the invention is directed to compounds of the following formula:



4

wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality.

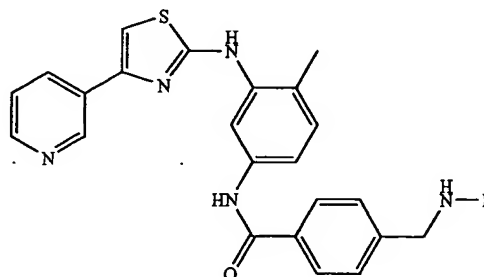
Among the particular compounds in which R<sub>1</sub> has the meaning as depicted in c) above, the invention is directed to amide-aniline compounds of the following formula:



wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality;

a —SO<sub>2</sub>—R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality; or a —CO—R or a —CO—NRR' group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

Among the particular compounds in which R<sub>1</sub> has the meaning as depicted in c) above, the invention is directed to amide-benzylamine compounds of the following formula:



wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing

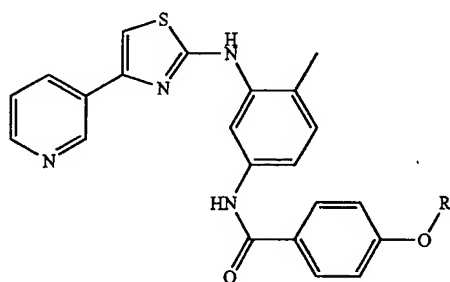


5

from 1 to 10 carbon atoms optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or an alkyl, cycloalkyl, aryl or heteroaryl group substituted by a

alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; a —SO<sub>2</sub>—R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a —CO—R or a —CO—NRR' group, wherein R and R' are independently chosen from H or an aryl heteroaryl, alkyl and cycloalkyl group optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality.

Among the particular compounds in which R1 has the meaning as depicted in c) above, the invention is directed to amide-phenol compounds of the following formula:



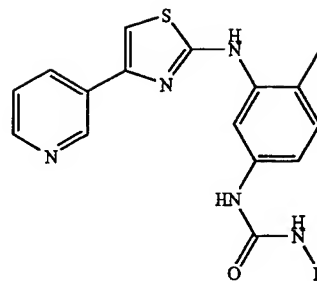
wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

a cycloalkyl, aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality; or an alkyl, cycloalkyl, aryl or heteroaryl group substituted by a alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality;

a —SO<sub>2</sub>—R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality; or a —CO—R or a —CO—NRR' group, wherein R and R' are independently chosen from H or an aryl, heteroaryl, alkyl and cycloalkyl group optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality.

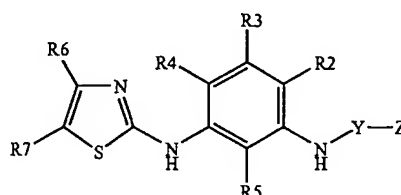
Among the particular compounds in which R1 has the meaning as depicted in c) above, the invention is directed to urea compounds of the following formula:

6



wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

Among the particular compounds in which R1 has the meaning as depicted in a) and b) above, the invention is directed to N-Aminoalkyl-N'-thiazol-2-yl-benzene-1,3-diamine compounds of the following formula:



wherein Y is a linear or branched alkyl group containing from 1 to 10 carbon atoms;

wherein Z represents an aryl or heteroaryl group, optionally substituted at one or more ring position with any permutation of the following groups:

a halogen such as F, Cl, Br, I;

a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

an O—R, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom,



9

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.

iv) H, a halogen selected from 1, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; and R<sup>7</sup> is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

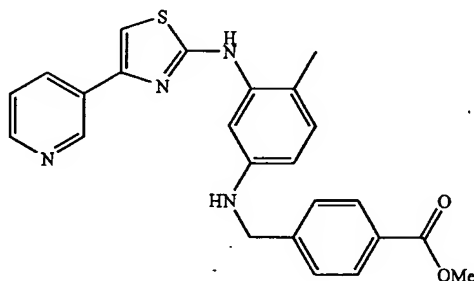
(ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.

iv) H, an halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

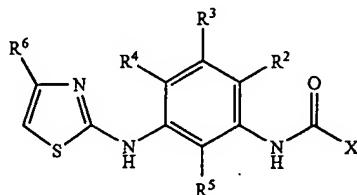
An example of preferred compounds of the above formula is depicted below:

001: 4-{[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylamino]-methyl}-benzoic acid methyl ester



Among the compounds of formula I, the invention is particularly embodied by the compounds of the following formula II:

FORMULA II



10

wherein X is R or NRR' and wherein R and R' are independently chosen from H, an aryl, a heteroaryl, an alkyl, or a cycloalkyl group optionally substituted with at least one heteroatom, such as for example a halogen chosen from F, I, Cl and Br and optionally bearing a pendant basic nitrogen functionality; or an aryl, a heteroaryl, an alkyl or a cycloalkyl group substituted with an aryl, a heteroaryl, an alkyl or a cycloalkyl group optionally substituted with at least one heteroatom, such as for example a halogen chosen from F, I, Cl and Br and optionally bearing a pendant basic nitrogen functionality,

R<sup>2</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>3</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>4</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>5</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>6</sup> is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

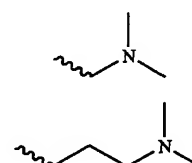
(ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.

iv) H, a halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

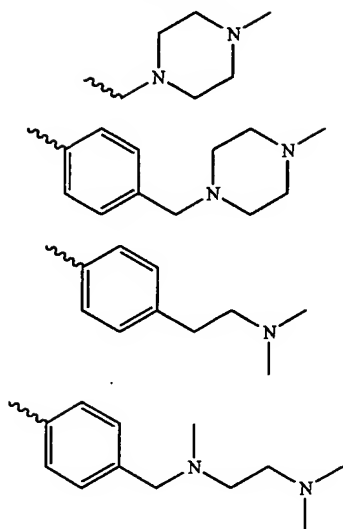
In another alternative, substituent R<sup>6</sup>, which in the formula II is connected to position 4 of the thiazole ring, may instead occupy position 5 of the thiazole ring.

Among the preferred compounds corresponding formula II, the invention is directed to compounds in which X is a substituted alkyl, aryl or heteroaryl group bearing a pendant basic nitrogen functionality represented for example by the structures a to f shown below, wherein the wavy line corresponds to the point of attachment to core structure of formula II:



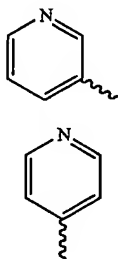
11

-continued



Among group a to f, X (see formula II) is preferentially group d.

Furthermore, among the preferred compounds of formula I or II, the invention concerns the compounds in which  $R^2$  and  $R^3$  are hydrogen. Preferentially,  $R^4$  is a methyl group and  $R^5$  is H. In addition,  $R^6$  is preferentially a 3-pyridyl group (cf. structure g below), or a 4-pyridyl group (cf. structure h below). The wavy line in structure g and h correspond to the point of attachment to the core structure of formula I or II.



Thus, the invention contemplates:

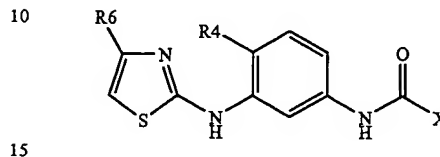
- 1—A compound of formula II as depicted above, wherein X is group d and  $R^6$  is a 3-pyridyl group.
- 2—A compound of formula II as depicted above, wherein X is group d and  $R^4$  is a methyl group.
- 3—A compound of formula I or II as depicted above, wherein  $R^1$  is group d and  $R^2$  is H.
- 4—A compound of formula I or II as depicted above, wherein  $R^1$  is group d and  $R^3$  is H.
- 5—A compound of formula I or II as depicted above, wherein  $R^1$  is group d and  $R^2$  and/or  $R^3$  and/or  $R^5$  is H.
- 6—A compound of formula I or II as depicted above, wherein  $R^6$  is a 3-pyridyl group and  $R^3$  is a methyl group.
- 7—A compound of formula I or II as depicted above, wherein  $R^6$  is a 3-pyridyl group and  $R^2$  is H.
- 8—A compound of formula I or II as depicted above, wherein  $R^2$  and/or  $R^3$  and/or  $R^5$  is H and  $R^4$  is a methyl group.

12

9—A compound of formula I or II as depicted above wherein  $R^2$  and/or  $R^3$  and/or  $R^5$  is H,  $R^4$  is a methyl group and  $R^6$  is a 3-pyridyl group.

Among the compounds of formula II, the invention is particularly embodied by the compounds wherein  $R^2$ ,  $R^3$ ,  $R^5$  are hydrogen, corresponding to the following formula II-1:

FORMULA II-1



wherein X is R or NRR' and wherein R and R' are independently chosen from H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a —SO<sub>2</sub>-R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a —CO—R or a —CO—NRR' group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

$R^4$  is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

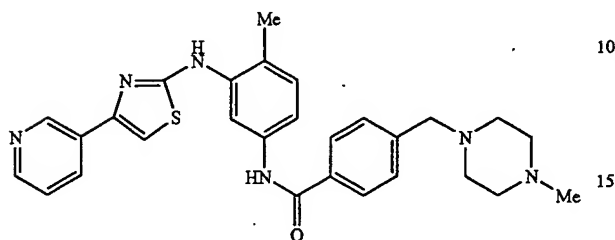
$R^6$  is one of the following:

- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.
- iv) H, a halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

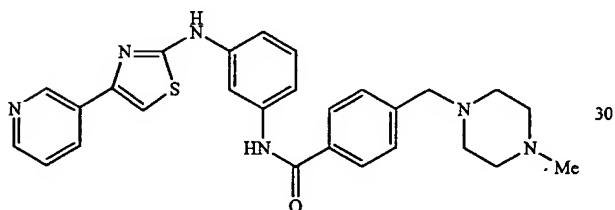
In another alternative, substituent  $R^6$ , which in the formula II is connected to position 4 of the thiazole ring, may instead occupy position 5 of the thiazole ring.

**13**  
EXAMPLES

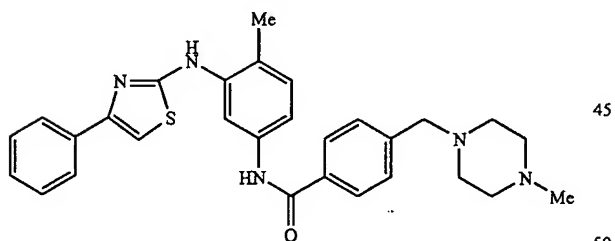
002: 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



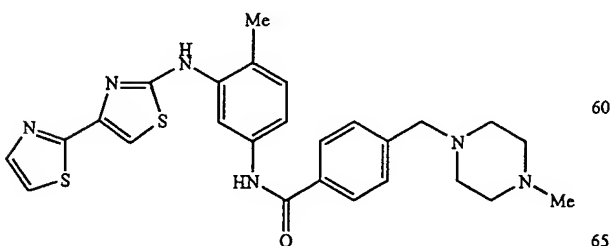
003: 4-(4-Methyl-piperazin-1-ylmethyl)-N-[3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



004: N-[4-Methyl-3-(4-phenyl-thiazol-2-ylamino)-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide

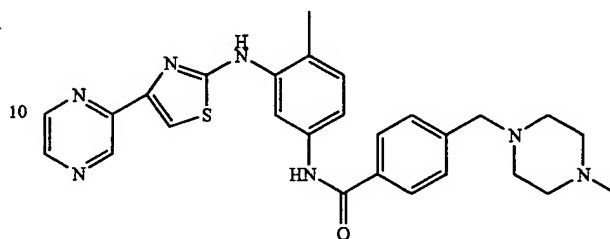


005: N-[3-([2,4']Bithiazolyl-2'-ylamino)-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide

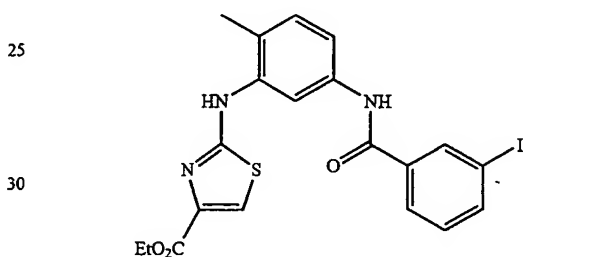


**14**

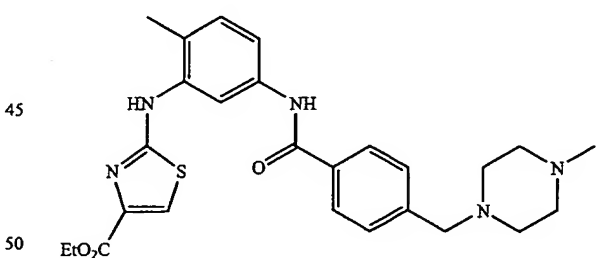
006: 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyrazin-2-yl-thiazol-2-ylamino)-phenyl]-benzamide



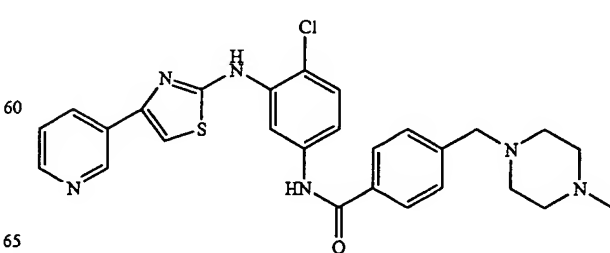
007: 2-[5-(3-Iodo-benzoylamino)-2-methyl-phenylamino]-thiazole-4-carboxylic acid ethyl ester



008: 2-{2-Methyl-5-[4-(4-methyl-piperazin-1-ylmethyl)-benzoylamino]-phenylamino}-thiazole-4-carboxylic acid ethyl ester

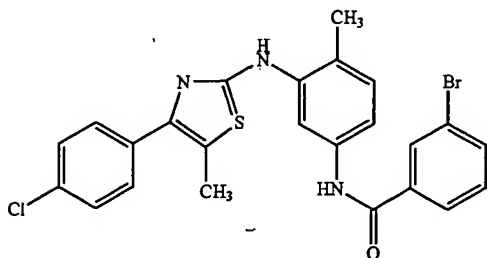


027: N-(4-chloro-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl)-4-(4-methyl-piperazin-1-ylmethyl)benzamide

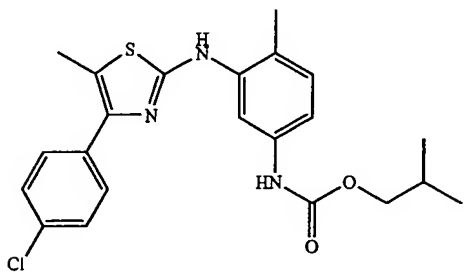


15

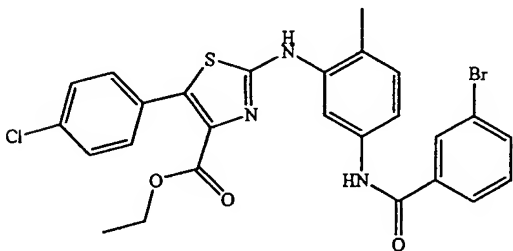
128: 3-Bromo-N-{3-[4-(4-chloro-phenyl)-5-methyl-thiazol-2-ylamino]-4-methyl-phenyl}-benzamide



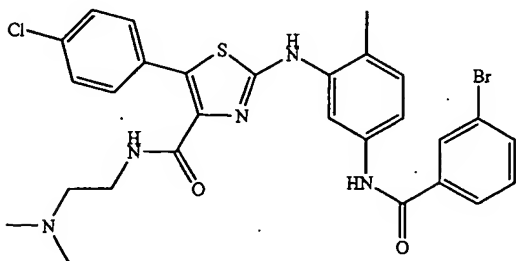
129: {3-[4-(4-Chloro-phenyl)-5-methyl-thiazol-2-ylamino]-4-methyl-phenyl}-carbamic acid isobutyl ester



130: 2-[5-(3-Bromo-benzoylamino)-2-methyl-phenylamino]-5-(4-chloro-phenyl)-thiazole-4-carboxylic acid ethyl ester



131: 2-[5-(3-Bromo-benzoylamino)-2-methyl-phenylamino]-5-(4-chloro-phenyl)-thiazole-4-carboxylic acid (2-dimethylamino-ethyl)-amide



16

110: N-{3-[4-(4-Methoxy-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide

5

10

15

20

25

30

35

40

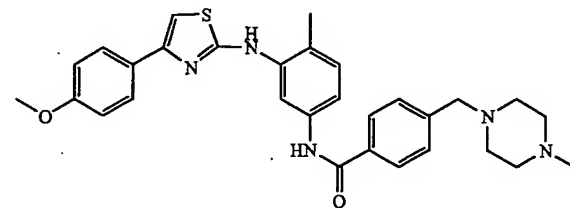
45

50

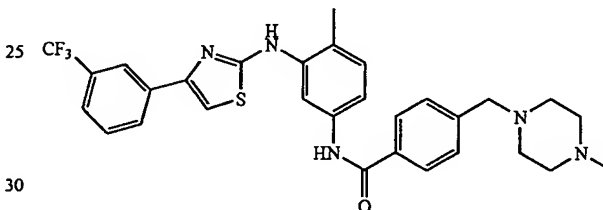
55

60

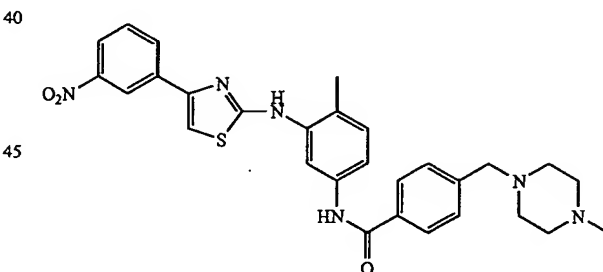
65



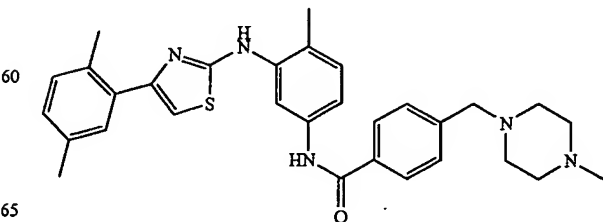
116: 4-(4-Methyl-piperazin-1-ylmethyl)-N-{4-methyl-3-[4-(3-trifluoromethyl-phenyl)-thiazol-2-ylamino]-phenyl}-benzamide



117: N-{4-Methyl-3-[4-(3-nitro-phenyl)-thiazol-2-ylamino]-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide

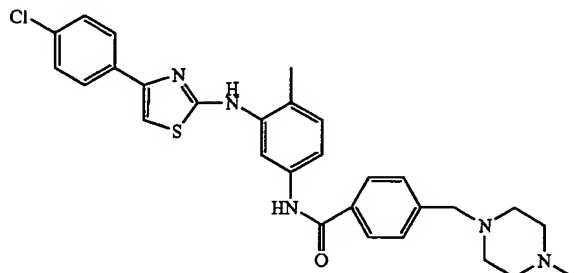


124: N-{3-[4-(2,5-Dimethyl-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide

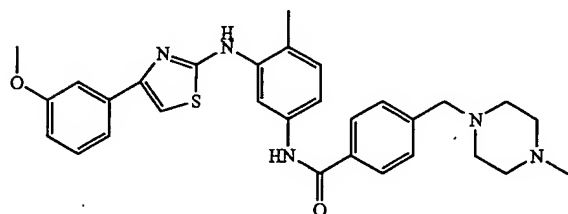


17

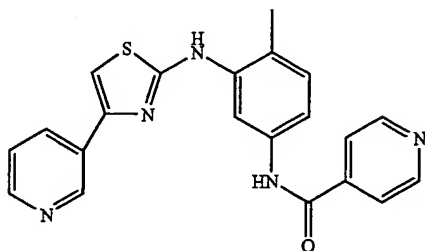
108: N-{3-[4-(4-Chloro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



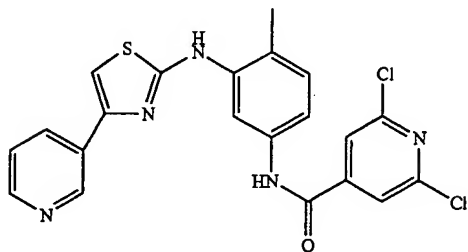
113: N-{3-[4-(3-Methoxy-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



063: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-isonicotinamide



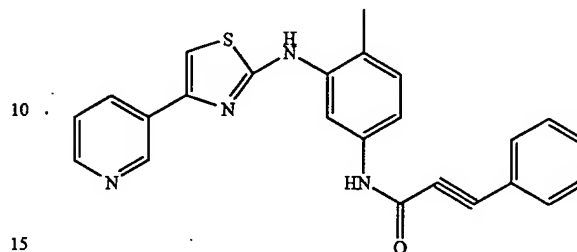
064: 2,6-Dichloro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-isonicotinamide



18

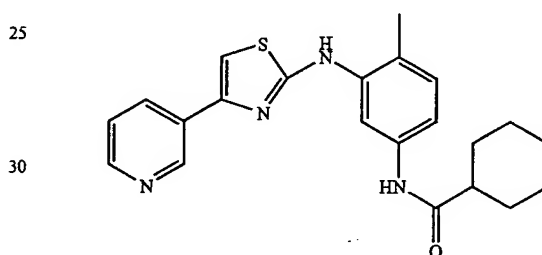
091: 3-Phenyl-propynoic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide

5



092: Cyclohexanecarboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide

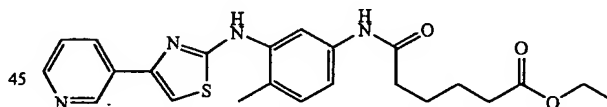
20



35

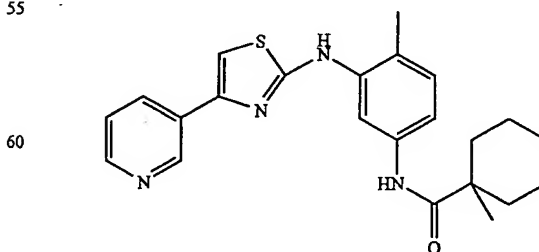
093: 5-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-pentanoic acid ethyl ester

40



094: 1-Methyl-cyclohexanecarboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide

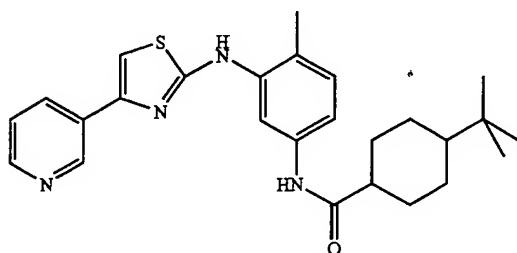
50



65

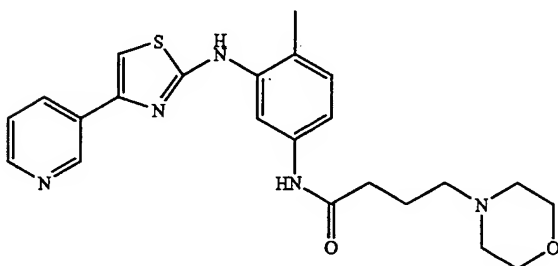
19

095: 4-tert-Butyl-cyclohexanecarboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide



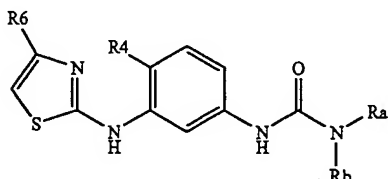
mixture of isomers  
cis/trans

096: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-morpholin-4-yl-butamide



beige powder mp: 116-120° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>)  
δ=1.80-2.00 (m, 2H); 2.29 (s, 3H); 2.30-2.45 (m, 6H); 3.55-3.65 (m, 6H); 7.15-7.25 (m, 2H); 7.46-7.50 (m, 2H); 7.52 (s, 1H); 8.35 (d, J=6.2 Hz, 1H); 8.55 (dd, J=1.5 Hz, J=4.7 Hz, 2H); 9.22 (s, 1H); 9.45 (s, 1H); 9.93 (s, 1H)

Among the compounds of formula II, the invention is particularly embodied by the compounds wherein X is a urea group, a —CO—NRR' group, corresponding to the [3-(thiazol-2-ylamino)-phenyl]-urea family and the following formula II-2:



FORMULA II-2

wherein Ra, Rb are independently chosen from H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

20

a —SO<sub>2</sub>-R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a —CO—R or a —CO—NRR' group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, or bearing a pendant basic nitrogen functionality.

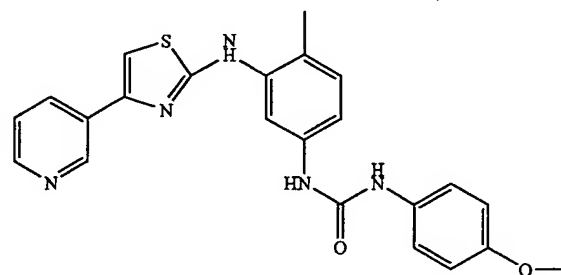
R<sup>4</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>6</sup> is one of the following:

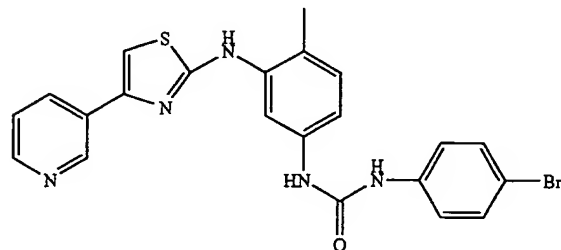
- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.
- iv) H, a halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

## EXAMPLES

009: 1-(4-Methoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



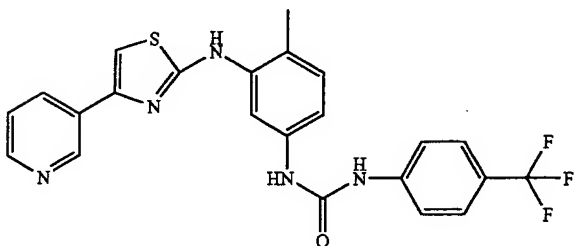
010: 1-(4-Bromo-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea





**21**

011: 1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(4-trifluoromethyl-phenyl)-urea



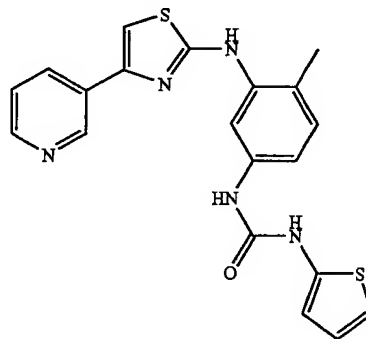
5

10

15

**22**

015: 1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-thiophen-2-yl-urea

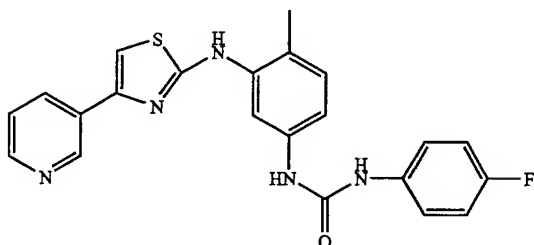


20

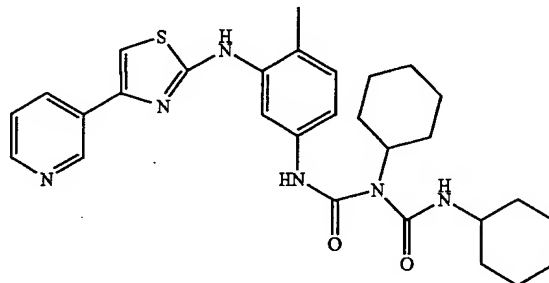
25

30

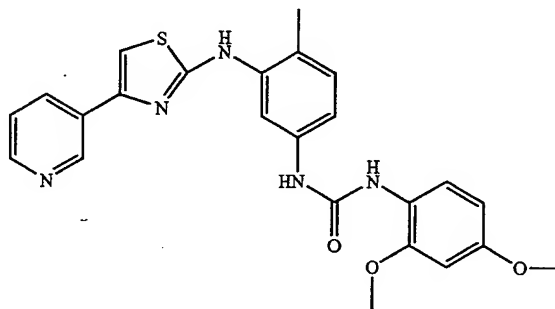
012: 1-(4-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



016: 1-Cyclohexyl-1-(N-Cyclohexy-formamide)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



017: 1-(2,4-Dimethoxy-phenyl)-3-[4-methyl-2-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

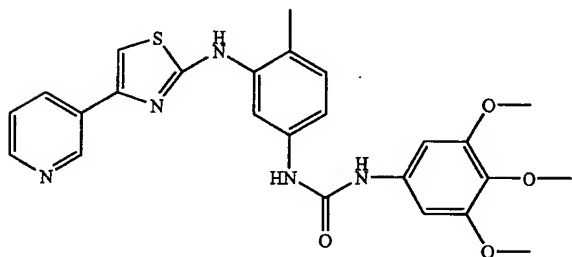


35

40

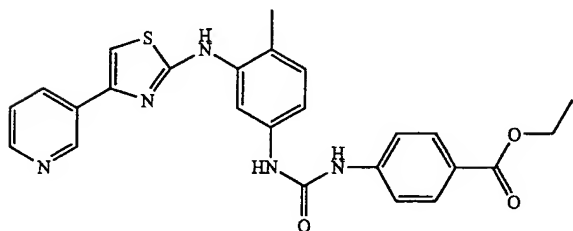
45

013: 1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(3,4,5-trimethoxy-phenyl)-urea



50

014: 4-{3-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-ureido}-benzoic acid ethyl ester

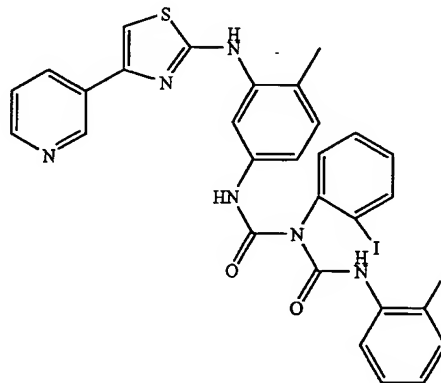


55

60

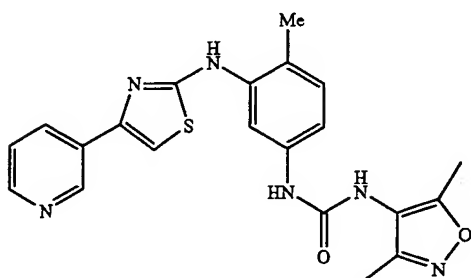
65

018: 1-(2-Iodo-phenyl)-1-(N-(2-Iodo-phenyl)-formamide)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

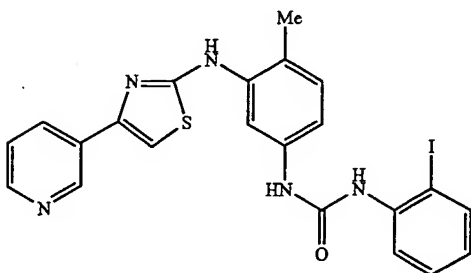


23

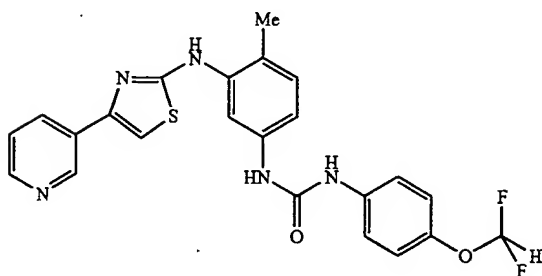
019: 1-(3,5-Dimethyl-isoxazol-4-yl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



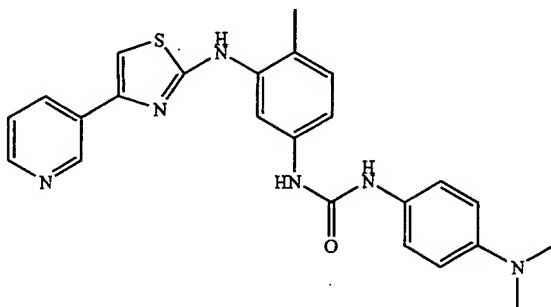
020: 1-(2-Iodo-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



021: 1-(4-Difluoromethoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

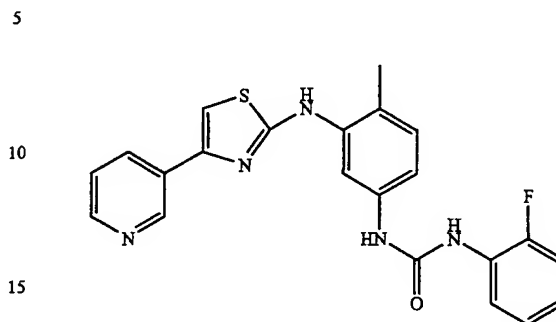


022: 1-(4-Dimethylamino-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



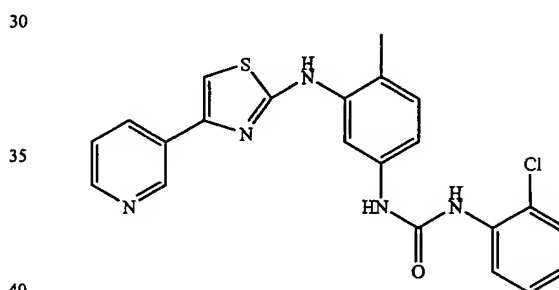
24

023: 1-(2-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

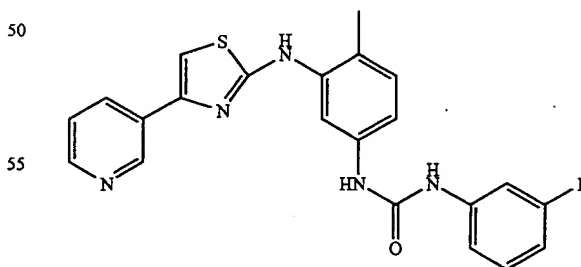


light brown powder mp: 203-206° C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ=2.24 (s, 3H); 6.98-7.00 (m, 2H); 7.10-7.23 (m, 3H); 7.40 (m, 1H); 7.48 (s, 1H); 8.25 (m, 1H); 8.37 (d, J=7.8 Hz, 1H); 8.51 (m, 3H); 9.03 (s, 1H); 9.19 (s, 1H); 9.39 (s, 1H)

024: 1-(2-Chloro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



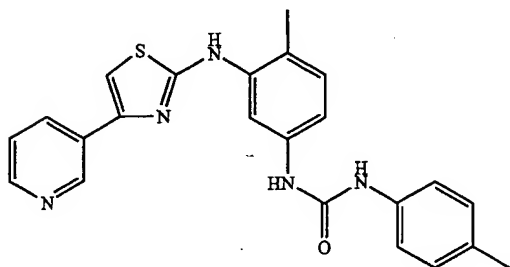
025: 1-(3-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



white powder mp: 210-215° C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.24 (s, 3H); 6.79 (t, J=6.3 Hz, 1H); 6.99 (m, 1H); 7.09-7.14 (m, 2H); 7.30 (m, 1H); 7.41 (t, J=4.7 Hz, 1H); 7.48 (s, 1H); 7.56 (d, J=1.2 Hz, 1H); 8.39 (d, J=8.0 Hz, 1H); 8.49-8.52 (m, 2H); 8.71 (s, 1H); 8.87 (s, 1H); 9.18 (s, 1H); 9.38 (s, 1H)

25

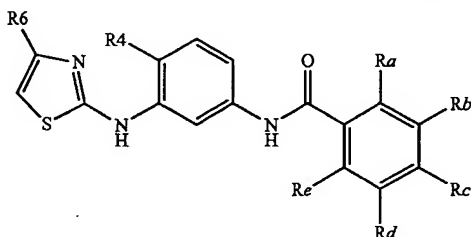
026: 1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-p-tolyl-urea



white powder mp: 238-240° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.29 (s, 3H); 2.31 (s, 3H); 7.05 (d, J=6.2 Hz, 1H); 7.10-1.16 (m, 3H); 7.42-7.49 (m, 3H); 7.53 (s, 1H); 8.35-8.62 (m, 5H); 9.22 (d, J=1.6 Hz, 1H); 9.43 (s, 1H)

Among the compounds of formula II, the invention is particularly embodied by the compounds wherein X is a substituted Aryl group, corresponding to the N-[3-(Thiazol-2-ylamino)-phenyl]-amide family and the following formula II-3:

FORMULA II-3



wherein Ra, Rb, Rc, Rd, Re are independently chosen from H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a —SO<sub>2</sub>-R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a —CO—R or a —CO—NRR' group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, and or bearing a pendant basic nitrogen functionality;

Ra, Rb, Rc, Rd, Re may also be a halogen such as I, Cl, Br and F

a NRR' group where R and R' are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a

26

cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

an OR group where R is H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; a —SO<sub>2</sub>-R' group wherein R' is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a NRaCORb group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a NRaCONRbRc group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a COOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

a CONRaRb, where Ra and Rb are a hydrogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at

27

least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

an  $\text{NHCOOR}$ , where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

an  $\text{OSO}_2\text{R}$ , where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

an  $\text{NRaOSO}_2\text{Rb}$ , where Ra and Rb are a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; Ra can also be a hydrogen; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

a CN group  
a trifluoromethyl group

$\text{R}^4$  is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

$\text{R}^6$  is one of the following:

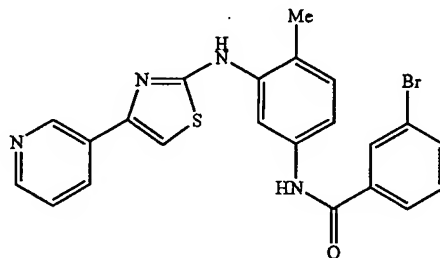
- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

28

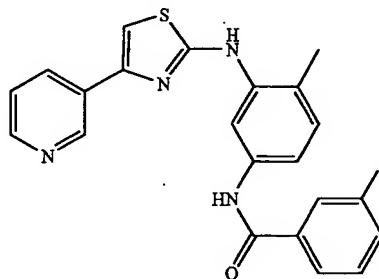
- iv) H, a halogen selected from I, F, Cl or Br,  $\text{NH}_2$ ,  $\text{NO}_2$  or  $\text{SO}_2\text{-R}$ , wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

## EXAMPLES

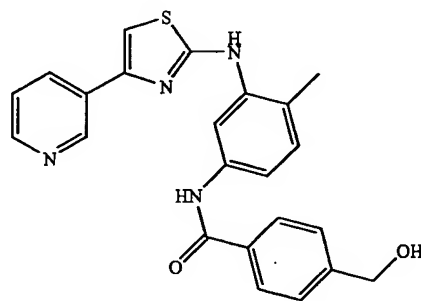
- 028: 3-Bromo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



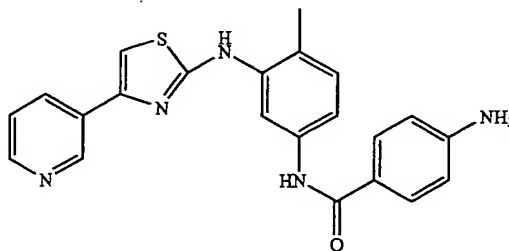
- 029: 3-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



- 030: 4-Hydroxymethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

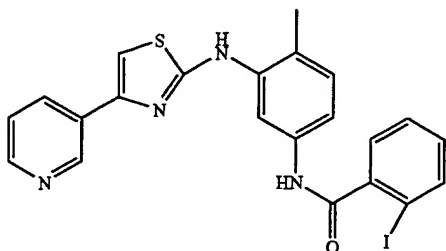


- 031: 4-Amino-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

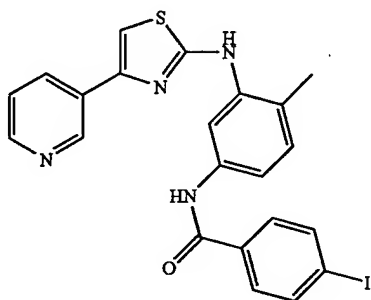


29

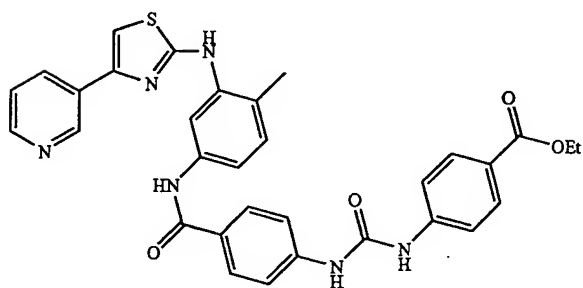
032: 2-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



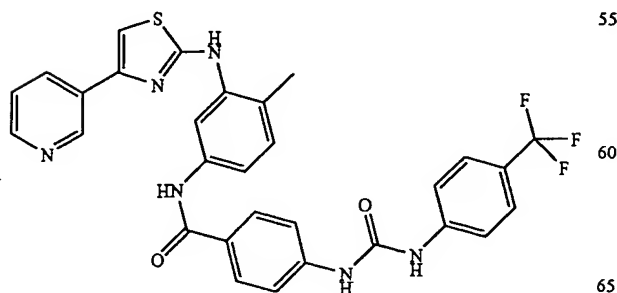
033: 4-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



034: 4-(3-{4-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]carbamoyl}-phenyl)-ureido)-benzoic acid ethyl ester

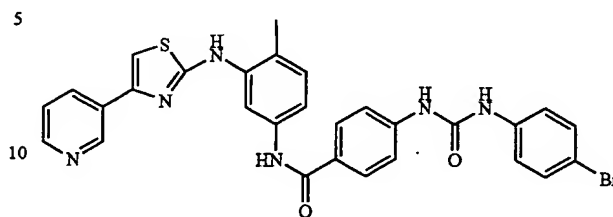


035: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide

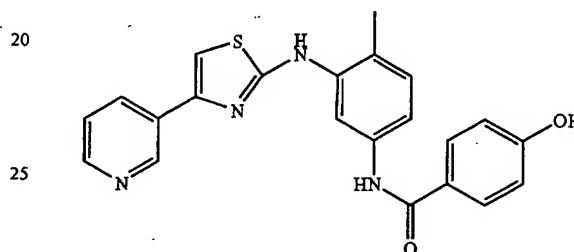


30

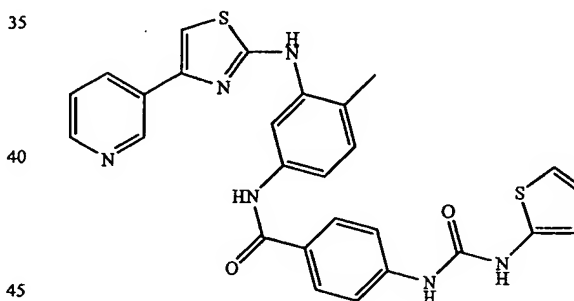
036: 4-[3-(4-Bromo-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



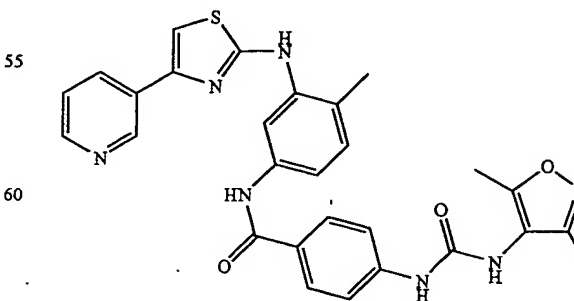
037: 4-Hydroxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



038: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-(3-thiophen-2-yl-ureido)-benzamide

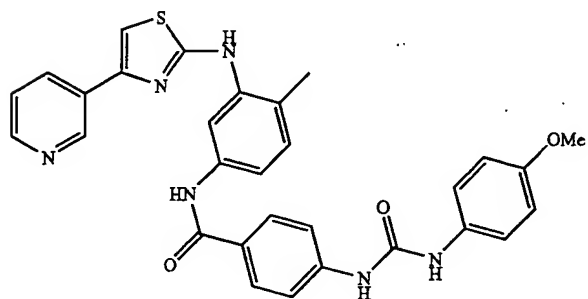


039: 4-[3-(3,5-Dimethyl-isoxazol-4-yl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



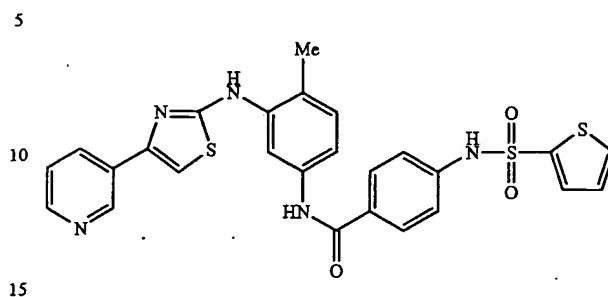
31

040: 4-[3-(4-Methoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

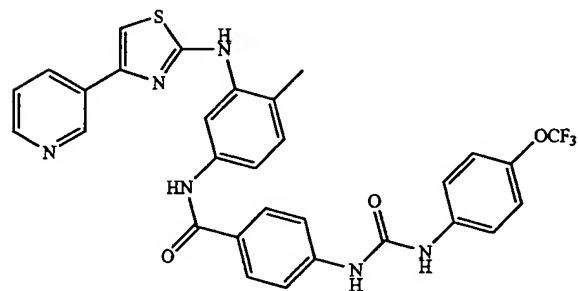


32

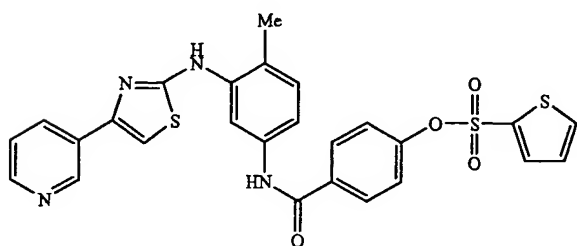
044: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]4-(thiophene-2-sulfonylamino)-benzamide



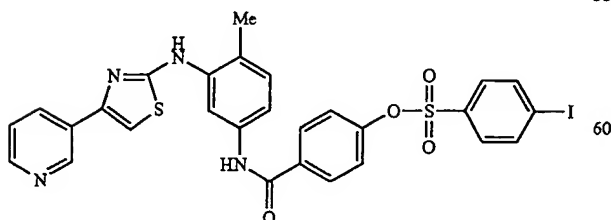
041: 4-[3-(4-Difluoromethoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



042: Thiophene-2-sulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester

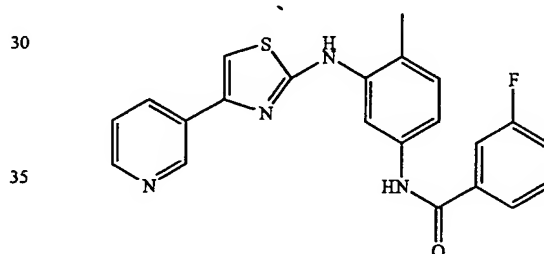


043: 4-Iodo-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester



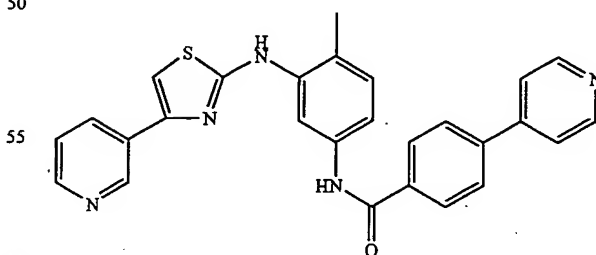
brown powder mp: 230-233° C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  
 δ=2.29 (s, 3H); 7.15-7.18 (m, 2H); 7.22-7.32 (m, 3H); 7.48  
 (m, 2H); 7.67 (dd, J=1.3 Hz, J=3.7 Hz, 1H); 7.90-7.96 (m,  
 3H); 8.38-8.42 (m, 1H); 8.51 (m, 1H); 8.57 (d, J=1.9 Hz, 1H);  
 9.17 (d, J=1.7 Hz, 1H); 9.44 (s, 1H); 10.12 (s, 1H); 10.82 (s,  
 1H)

045: 3-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



off-white foam mp: 184-186° C. <sup>1</sup>H NMR (CD<sub>3</sub>OD-d<sub>4</sub>):  
 δ=2.23 (s, 3H); 7.12-7.14 (m, 2H); 7.20-7.23 (m, 2H); 7.30  
 (m, 1H); 7.43 (m, 1H); 7.50 (m, 1H); 7.66 (d, J=1.0 Hz, 1H);  
 8.23 (m, 1H); 8.33 (m, 1H); 8.38 (s, 1H); 8.98 (s, 1H)

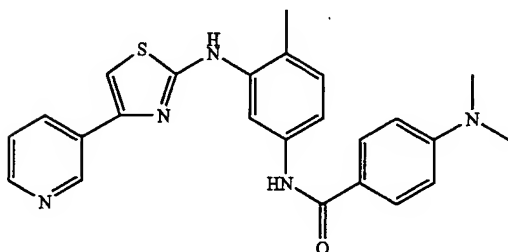
046: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-pyridin-4-yl-benzamide



yellow powder mp: 254-256° C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ  
 2.34 (s, 3H); 7.28 (d, J=8.0 Hz, 1H); 7.45-7.49 (m, 2H); 7.54  
 (s, 1H); 7.78 (t, J=7.6 Hz, 1H); 7.89-7.91 (m, 2H); 8.10 (t,  
 J=7.8 Hz, 2H); 8.37-8.42 (m, 2H); 8.55 (d, J=4.7 Hz, 1H);  
 8.73-8.77 (m, 3H); 9.24 (s, 1H); 9.52 (s, 1H); 10.43 (s, 1H)

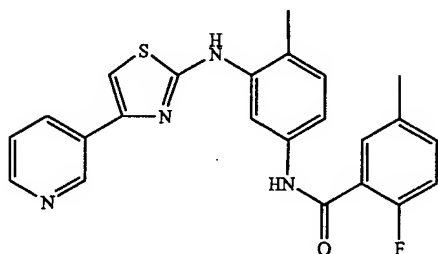
33

047: 4-Dimethylamino-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



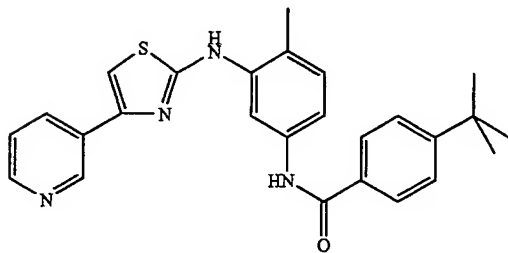
beige powder mp: 147-150° C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.25 (s, 3H); 2.99 (s, 6H); 6.76 (d, J=8.9 Hz, 2H); 7.16 (d, J=8.3 Hz, 1H); 7.35 (d, J=2.0 Hz, 1H); 7.44-7.47 (m, 2H); 7.86-7.89 (m, 2H); 8.34-8.36 (m, 1H); 8.48-8.50 (m, 1H); 8.56-8.57 (m, 1H); 9.16 (s, 1H); 9.44 (s, 1H); 9.85 (s, 1H)

048: 2-Fluoro-5-methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



brown orange powder mp: 103-106° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.26 (s, 3H); 2.35 (s, 3H); 7.17-7.47 (m, 7H); 8.29 (dd, J=1.6 Hz, J=7.9 Hz, 1H); 8.47 (d, J=3.5 Hz, 1H); 8.57 (s, 1H); 9.15 (d, J=2.0 Hz, 1H); 9.44 (s, 1H); 10.33 (s, 1H)

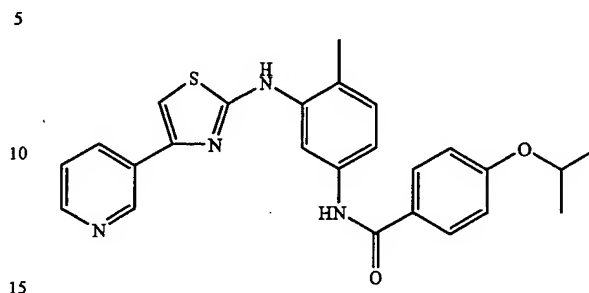
049: 4-tert-Butyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



brown powder mp: 145-150° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=1.32 (s, 9H); 2.04 (s, 3H); 7.18 (d, J=8.4 Hz, 1H); 7.35-7.44 (m, 2H); 7.46 (s, 1H); 7.55 (d, J=8.5 Hz, 1H); 7.90 (d, J=8.5 Hz, 1H); 8.32 (d, J=7.9 Hz, 1H); 8.47 (dd, J=1.5 Hz, J=4.7 Hz, 1H); 8.60 (d, J=2.0 Hz, 1H); 9.15 (d, J=1.7 Hz, 1H); 9.43 (s, 1H); 10.15 (s, 1H)

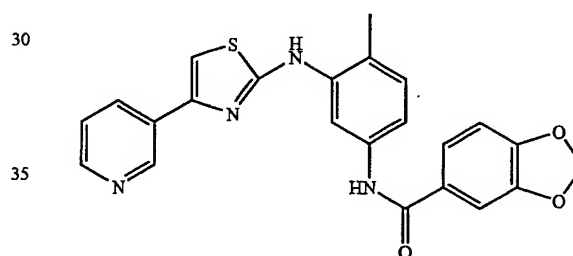
34

050: 4-Isopropoxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



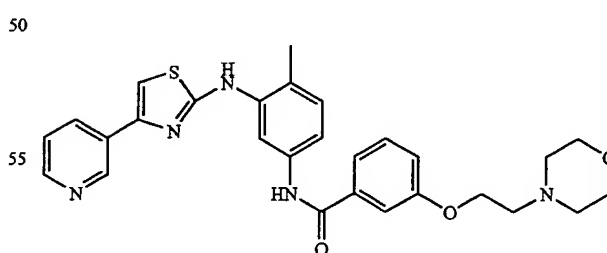
brown powder mp: 154-155° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=1.34 (d, J=5.9 Hz, 6H); 4.72 (hept, J=5.9 Hz, 1H); 7.01 (d, J=7.0 Hz, 2H); 7.18 (d, J=8.5 Hz, 1H); 7.35-7.44 (m, 2H); 7.46 (s, 1H); 7.94 (dd, J=2.0 Hz, J=6.7 Hz, 2H); 8.32 (d, J=8.3 Hz, 1H); 8.48 (dd, J=3.3 Hz, J=4.8 Hz, 1H); 8.58 (d, J=2.0 Hz, 1H); 9.15 (d, J=1.8 Hz, 1H); 9.43 (s, 1H); 10.4 (s, 1H)

051: Benzo[1,3]dioxole-5-carboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide



brown orange powder mp: 130-132° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.23 (s, 3H); 6.10 (s, 2H); 7.03 (d, J=8.1 Hz, 1H); 7.15 (d, J=8.3 Hz, 1H); 7.25-7.55 (m, 6H); 8.26 (s, 1H); 8.45 (dd, J=1.5 Hz, J=4.7, 1H); 8.55 (d, J=2.0 Hz, 1H); 9.12 (d, J=1.7 Hz, 1H); 9.40 (s, 1H); 10.01 (s, 1H)

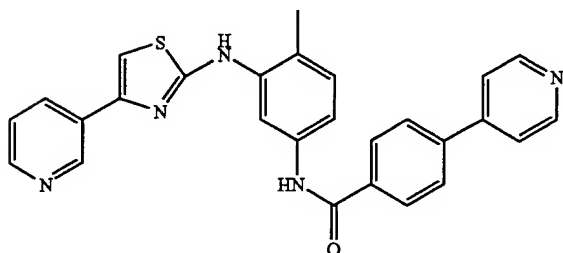
052: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(2-morpholin-4-yl-ethoxy)-benzamide



beige yellow powder mp: 75-80° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.10-2.25 (m, 4H); 2.50-2.60 (m, 2H); 3.19 (s, 3H); 3.41-3.48 (m, 4H); 4.00-4.06 (m, 2H); 7.00-7.11 (m, 2H); 7.22-7.35 (m, 6H); 8.18 (d, J=8.0 Hz, 1H); 8.33 (d, J=0.9 Hz, 1H); 8.49 (d, J=1.7 Hz, 1H); 9.03 (s, 1H); 9.31 (s, 1H); 10.05 (s, 1H)

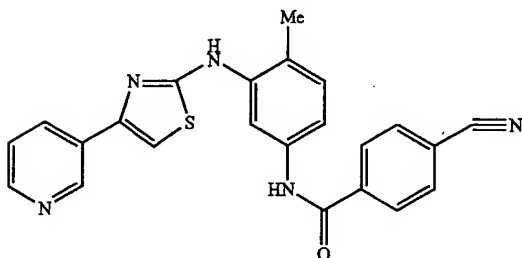
35

053: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-pyridin-4-yl-benzamide

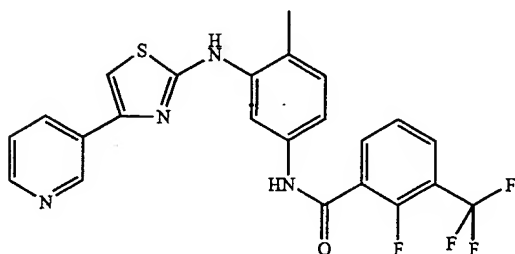


brown powder mp: dec. 250° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.28 (s, 3H); 7.21 (d, J=7.9 Hz, 1H); 7.30-7.50 (m, 3H) 7.81 (d, J=4.7 Hz, 1H); 7.98 (d, J=7.5 Hz, 2H); 8.13 (d, J=7.9 Hz, 2H); 8.32 (d, J=7.7 Hz, 1H); 8.48 (d, J=4.9 Hz, 1H); 8.62-8.69 (m, 3H); 9.16 (s, 1H); 9.45 (s, 1H) 10.34 (s, 1H)

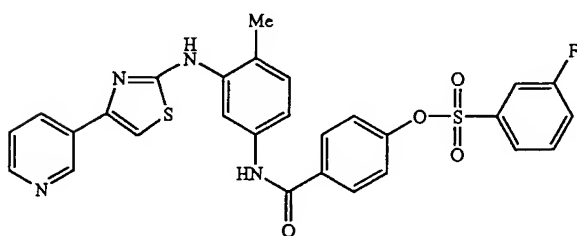
054: 3-Cyano-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



055: 2-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide

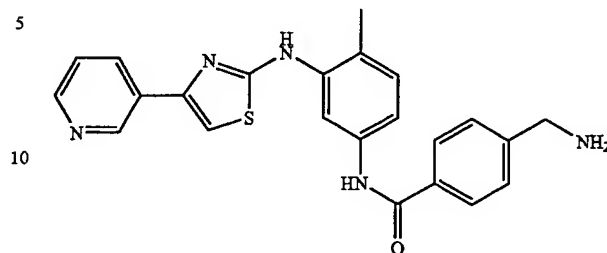


056: 3-Fluoro-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester

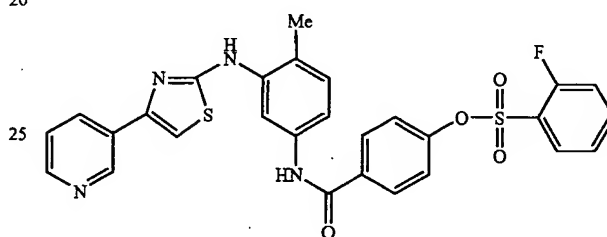


36

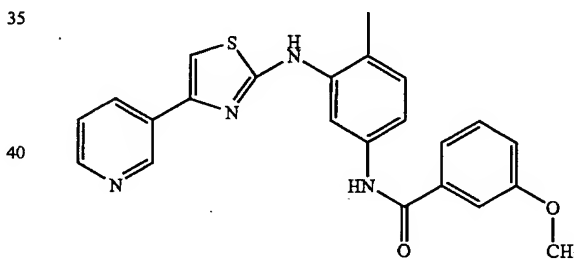
057: 4-Aminomethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



058: 2-Fluoro-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester

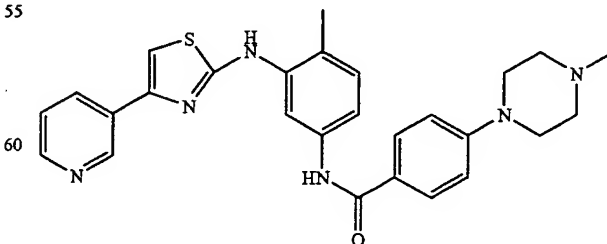


059: 3-Methoxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



white powder mp: 76-79° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.32 (s, 3H); 3.89 (s, 3H); 7.22-7.25 (m, 2H); 7.44-7.58 (m, 4H); 8.28-8.35 (m, 1H); 8.52 (dd, J=1.6 Hz, J=4.7 Hz, 1H); 8.66 (d, J=2.0 Hz, 1H); 9.20 (d, J=1.4 Hz, 1H); 9.50 (s, 1H); 10.25 (s, 1H)

060: 4-(4-Methyl-piperazin-1-yl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-benzamide



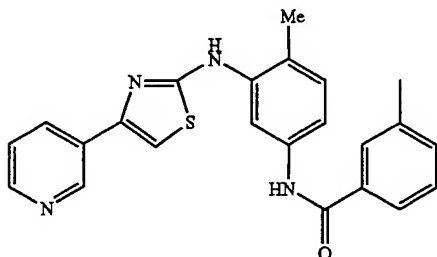
beige brown powder mp: 128-130° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.15 (s, 3H); 2.18 (s, 3H); 2.35-2.41 (m, 4H); 3.18-



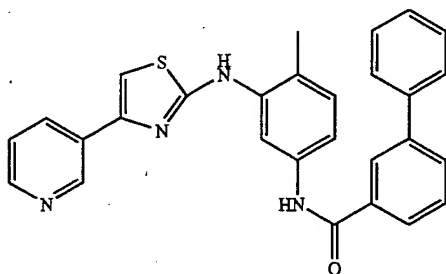
37

3.3.24 (m, 4H); 6.94 (d, J=8.9 Hz, 2H); 7.09 (d, J=8.4 Hz, 1H); 7.28-7.38 (m, 3H); 7.81 (d, J=8.9 Hz, 2H); 8.20-8.25 (m, 1H); 8.40 (dd, J=1.6 Hz, J=4.7, 1H); 8.48 (d, J=1.9 Hz, 1H); 9.07 (d, J=1.5 Hz, 1H); 9.35 (s, 1H); 9.84 (s, 1H)

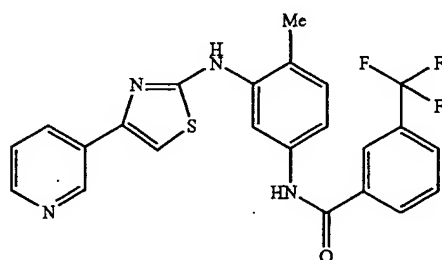
061: 3-Methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



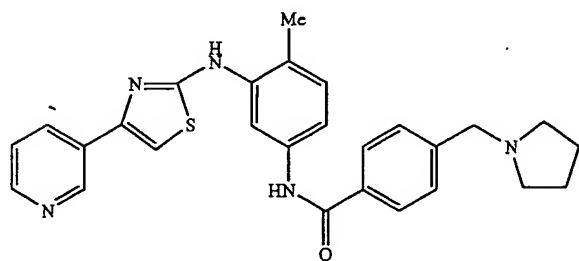
062: Biphenyl-3-carboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide



065: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide

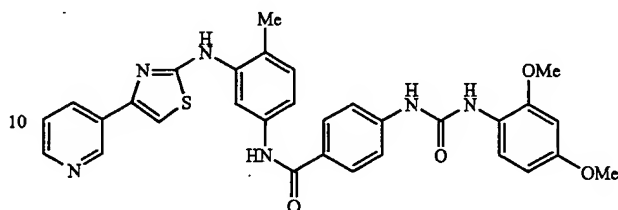


099: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-pyrrolidin-1-ylmethyl-benzamide

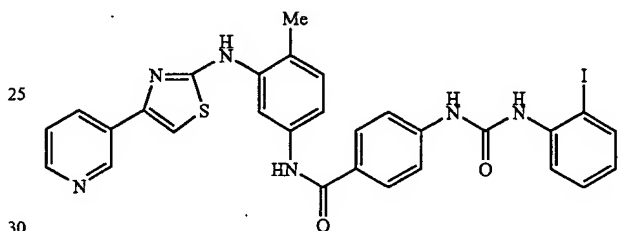


38

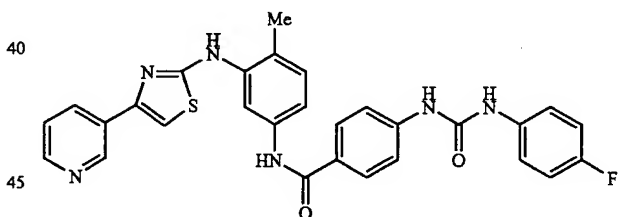
100: 4-[3-(2,4-Dimethoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



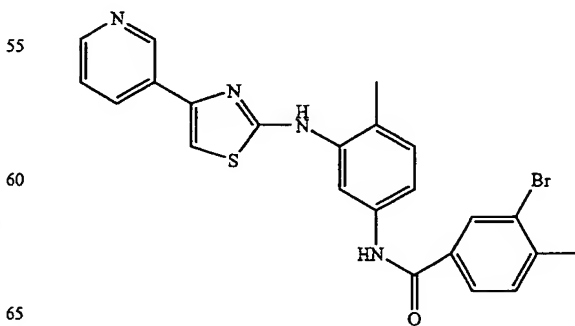
101: 4-[3-(2-Iodo-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



102: 4-[3-(4-Fluoro-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

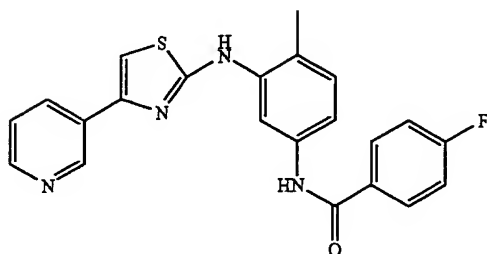


105: 3-Bromo-4-methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

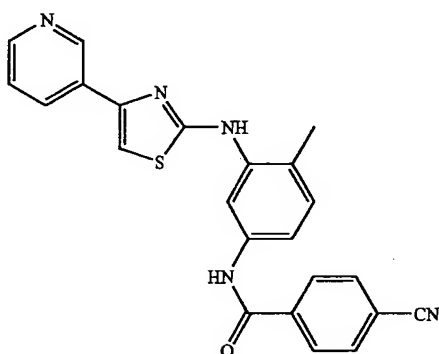


39

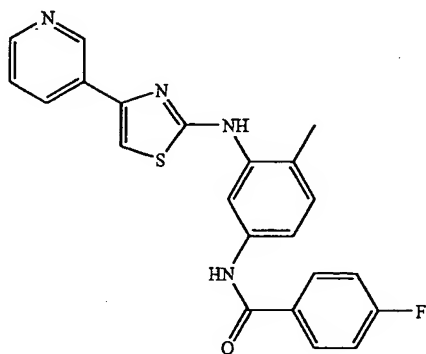
106: 4-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



103: 4-Cyano-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



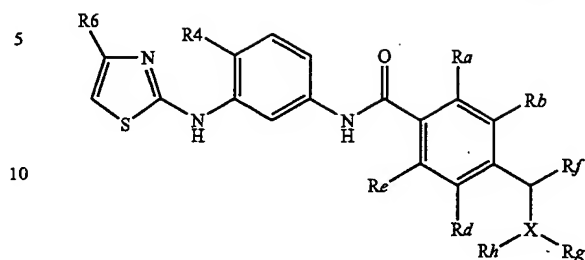
104: 4-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



Among compounds of formula II, the invention is particularly embodied by the compounds wherein X is a substituted-aryl group, corresponding to the 4-(4-substituted-1-ylmethyl)-N-[3-(thiazol-2-ylamino)-phenyl]-benzamide family and the following formula II-4:

40

FORMULA II-4



wherein X is a heteroatom, such as O or N

wherein Ra, Rb, Rd, Re, Rf, Rg, Rh are independently chosen from H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

or a NRR' group where R and R' are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or an OR group where R is H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; a —SO<sub>2</sub>-R' group wherein R' is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

or a NRaCORb group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with

41

an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a  $\text{NRaCONRbRc}$  group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a COOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a CONRaRb, where Ra and Rb are a hydrogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or an NHCOOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or an  $\text{OSO}_2\text{R}$ , where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

42

or an  $\text{NRaOSO}_2\text{Rb}$ , where Ra and Rb are a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; Ra can also be a hydrogen; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

or a  $\text{—SO}_2\text{—R}$  group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a  $\text{—CO—R}$  or a  $\text{—CO—NRR'}$  group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

Ra, Rb, Rd, Re can also be halogen such as Cl, F, Br, I or trifluoromethyl;

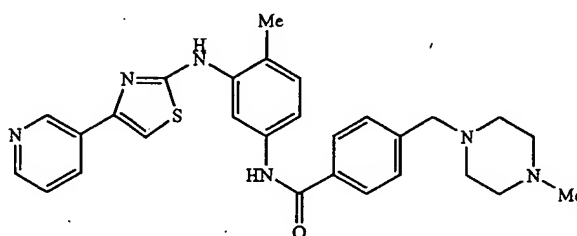
$\text{R}^4$  is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

$\text{R}^6$  is one of the following:

- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- iv) H, a halogen selected from I, F, Cl or Br;  $\text{NH}_2$ ,  $\text{NO}_2$  or  $\text{SO}_2\text{—R}$ , wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

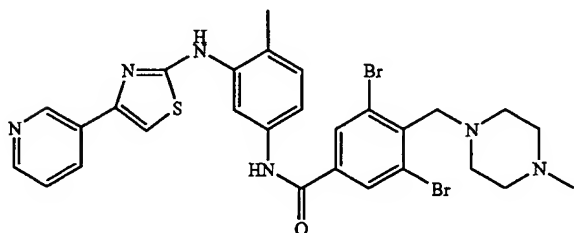
## EXAMPLES

066: 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

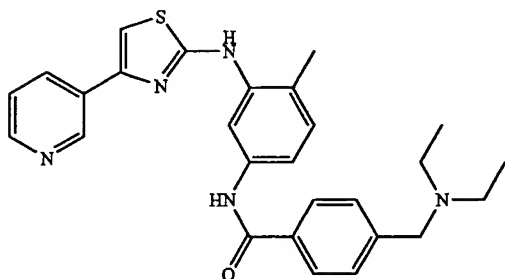


43

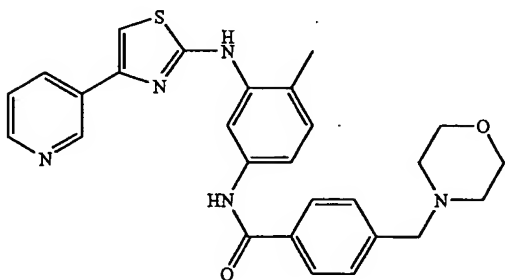
067: 3,5-Dibromo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



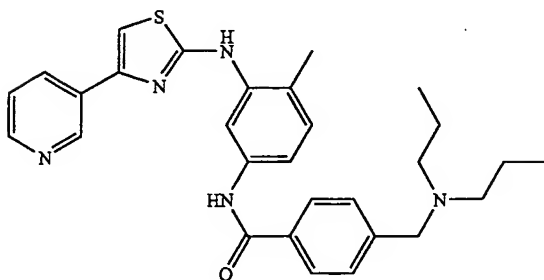
068: 4-Diethylaminomethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



069: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-morpholin-4-ylmethyl-benzamide

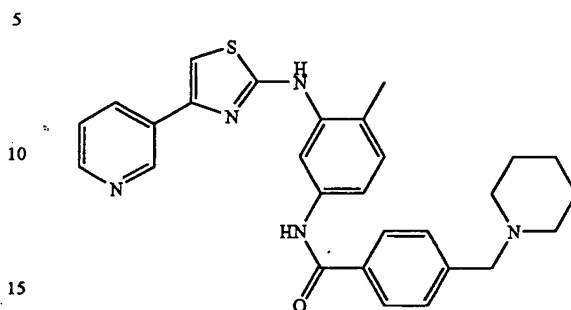


070: 4-Dipropylaminomethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

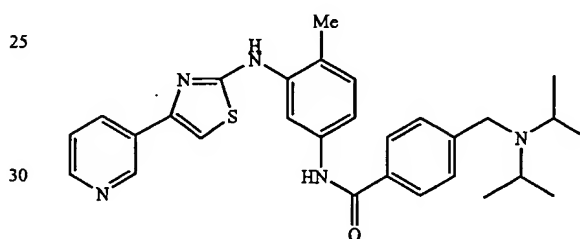


44

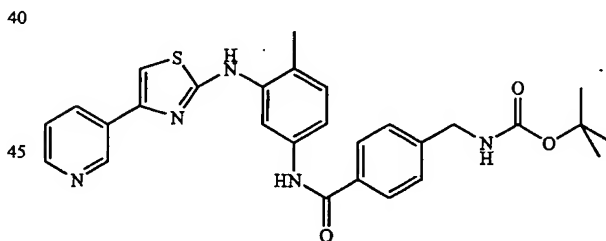
071: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-piperidin-1-ylmethyl-benzamide



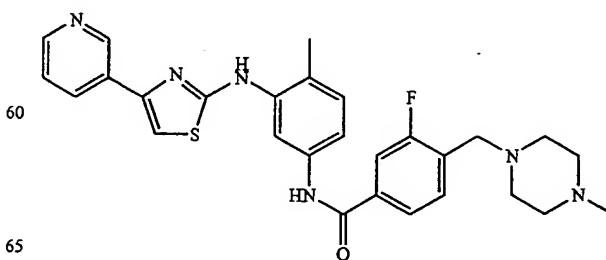
072: 4-[(Diisopropylamino)-methyl]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



073: {4-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-benzyl}-carbamic acid tert-butyl ester

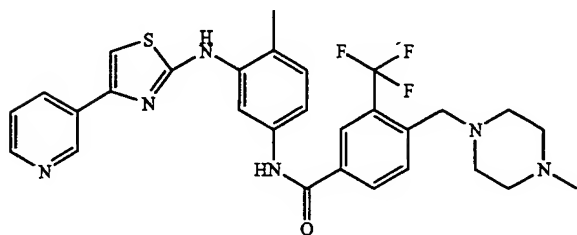


074: 3-Fluoro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



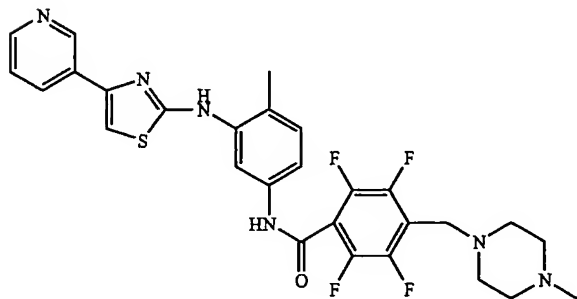
45

075: 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide

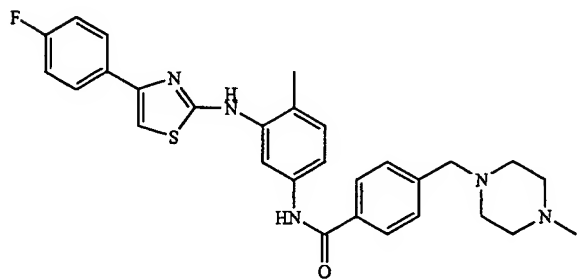


yellow crystals mp: 118-120° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.22 (s, 3H); 2.33 (s, 3H); 2.34-2.50 (m, 8H); 3.74 (s, 2H); 7.26 (d, J=8.3 Hz, 1H); 7.41-7.49 (m, 2H); 7.53 (s, 1H); 7.99 (d, J=8.0 Hz, 1H); 8.28-8.31 (m, 2H); 8.38 (d, J=7.9 Hz, 1H); 8.53 (dd, J=1.3 Hz, J=4.7 Hz, 1H); 8.68 (d, J=1.9 Hz, 1H); 9.21 (d, J=2.0 Hz, 1H); 9.53 (s, 1H); 10.49 (s, 1H)

076: 2,3,5,6-Tetrafluoro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

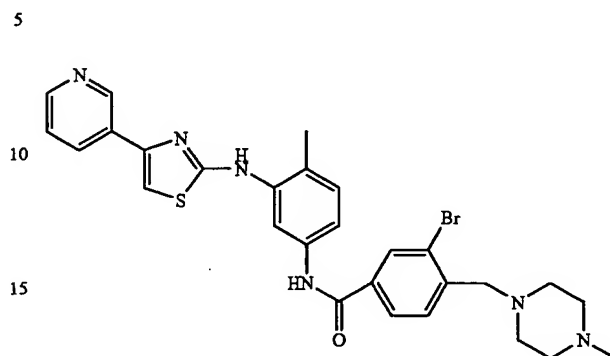


077: N-{3-[4-(4-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide

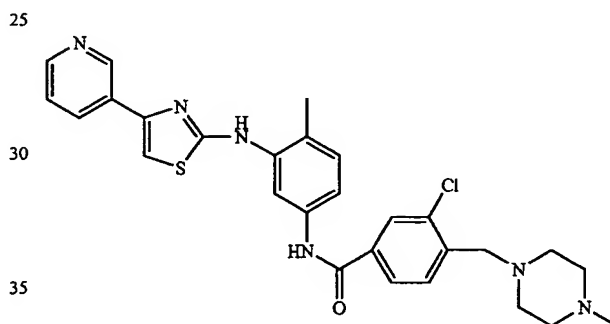


46

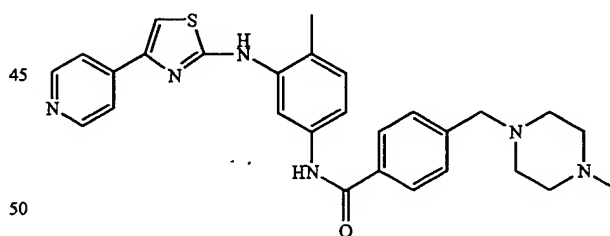
078: 3-Bromo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



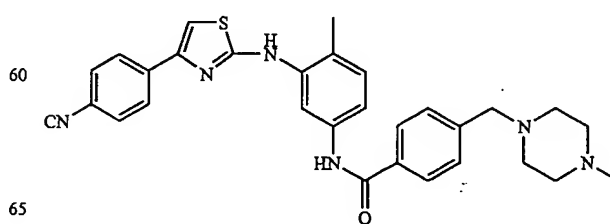
079: 3-Chloro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



080: 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-4-yl-thiazol-2-ylamino)-phenyl]-benzamide

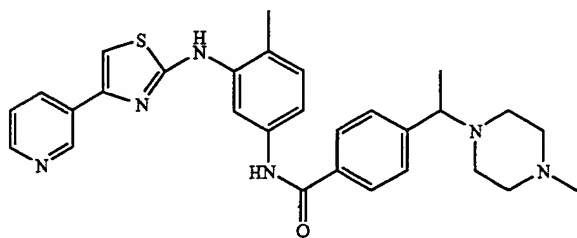


081: N-{3-[4-(4-Cyano-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



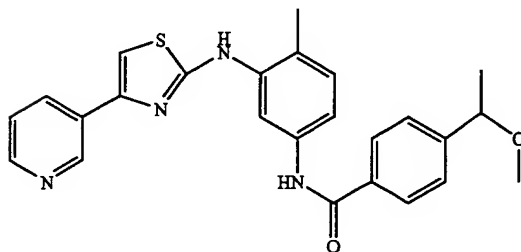
47

082: 4-[1-(4-Methyl-piperazin-1-yl)-ethyl]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

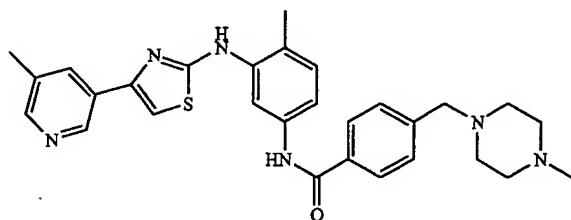


beige powder mp: 153-155° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>)  
 $\delta$ =1.29 (d, J=6.6 Hz, 3H); 2.15 (s, 3H); 2.26 (s, 3H); 3.15-3.25 (m, 9H); 7.18 (d, J=8.4 Hz, 1H); 7.35-7.47 (m, 5H); 7.91 (d, J=8.2 Hz, 2H); 8.31 (d, J=8.0 Hz, 1H); 8.47 (dd, J=1.6 Hz, J=4.7 Hz, 1H); 8.60 (d, J=2.0, 1H); 9.15 (d, J=0.6, 1H); 9.45 (s, 1H); 10.18 (s, 1H)

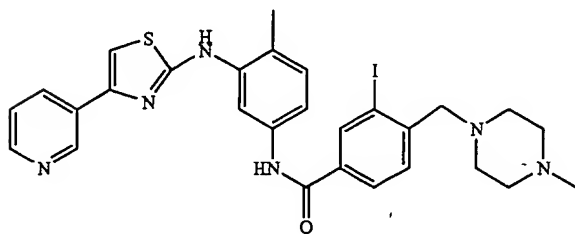
083: 4-(1-Methoxy-ethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



084: N-[4-Methyl-3-[4-(5-methyl-pyridin-3-yl)-thiazol-2-ylamino]-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide

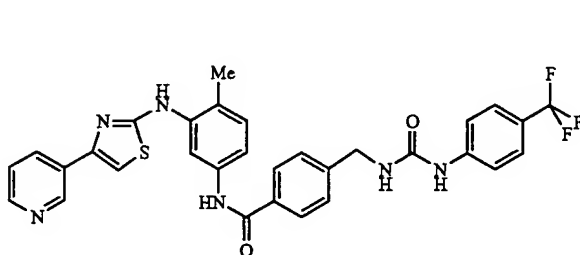


085: 3-Iodo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

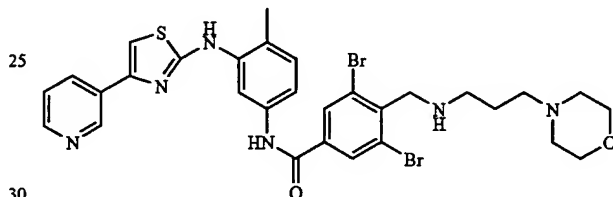


48

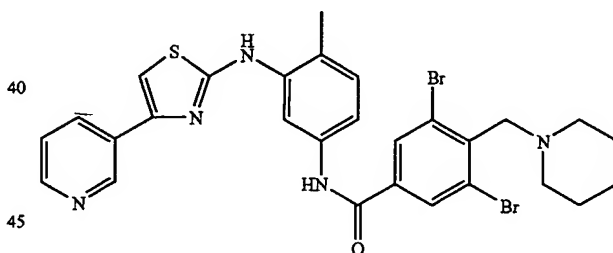
086: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[3-(4-trifluoromethyl-phenyl)-ureidomethyl]-benzamide



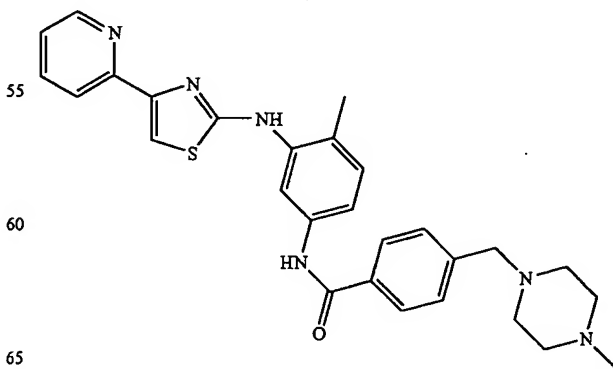
087: 3,5-Dibromo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[(3-morpholin-4-yl-propylamino)-methyl]-benzamide



107: 3,5-Dibromo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-piperidin-1-ylmethyl-benzamide

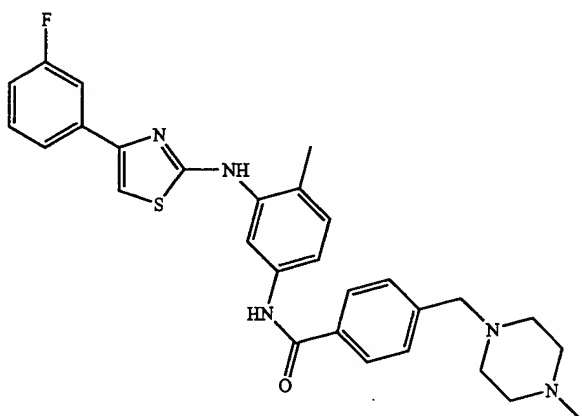


122: 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-2-yl-thiazol-2-ylamino)-phenyl]-benzamide

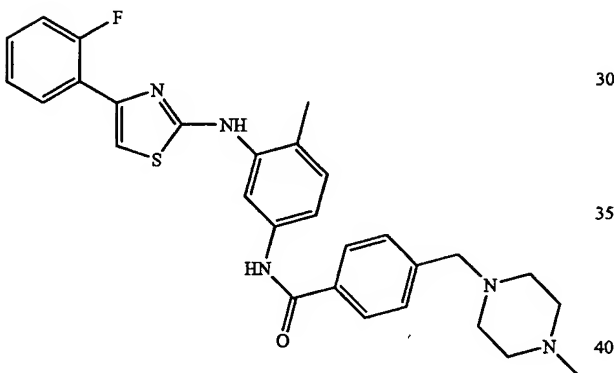


49

111: N-{3-[4-(3-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide

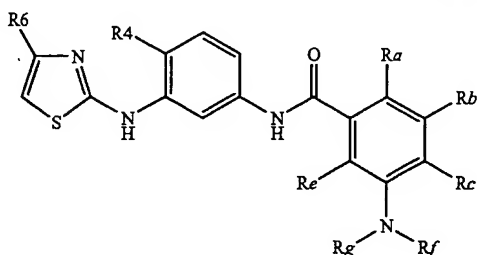


118: N-{3-[4-(2-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl}-4-(4-methyl-piperazin-1-ylmethyl)-benzamide



Among compounds of formula II, the invention is particularly embodied by the compounds wherein X is a-aryl-substituted group, corresponding to the 3-Disubstituted-amino-N-[3-(thiazol-2-ylamino)-phenyl]-benzamide family and the following formula II-5:

FORMULA II-5



wherein Ra, Rb, Rc, Re, Rf, Rg are independently chosen from H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a

50

cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

or a NRR' group where R and R' are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or an OR group where R is H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; a —SO<sub>2</sub>-R' group wherein R' is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

or a NRaCORb group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a NRaCONRbRc group where Ra and Rb are H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

or a COOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom,

51

notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

or a CONRaRb, where Ra and Rb are a hydrogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

or an NHCOOR, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

an OSO<sub>2</sub>R, where R is a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

or an NRaOSO<sub>2</sub>Rb, where Ra and Rb are a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example a halogen) and/or bearing a pendant basic nitrogen functionality; Ra can also be a hydrogen; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality;

or a —SO<sub>2</sub>—R group wherein R is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a —CO—R or a —CO—NRR' group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at

52

least one heteroatom, notably selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality. Ra, Rb, Rc, Re can also be halogen such as Cl, F, Br, I or trifluoromethyl;

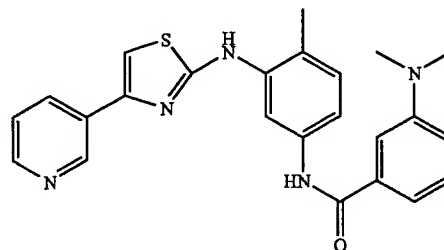
R<sup>4</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>6</sup> is one of the following:

- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- iv) H, a halogen selected from I, F, Cl or Br, NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>—R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

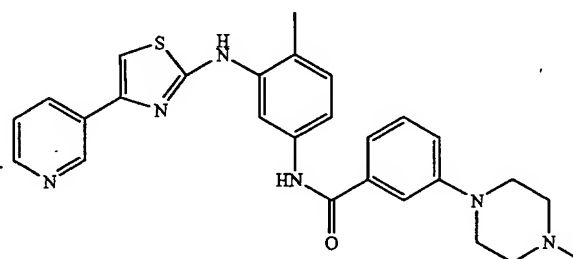
## EXAMPLES

088: 3-Dimethylamino-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



beige powder mp: 197-198° C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ=2.32 (s, 3H); 3.03 (s, 6H); 6.97 (d, J=6.4 Hz, 1H); 7.23-7.56 (m, 7H); 8.37 (d, J=7.3 Hz, 1H); 8.53 (d, J=4.7 Hz, 1H); 8.63 (s, 1H); 9.20 (s, 1H); 9.48 (s, 1H); 10.15 (s, 1H)

089: 3-(4-Methyl-piperazin-1-yl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide



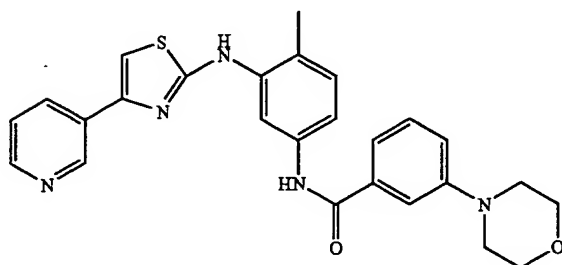
beige powder mp: 274-246° C. <sup>1</sup>H RMN (DMSO-d<sub>6</sub>) δ=2.23 (s, 3H); 2.24-2.30 (m, 4H); 3.22-3.27 (m, 4H); 7.07-



53

7.20 (m, 2H); 7.36-7.53 (m, 6H); 8.31 (d, J=7.5 Hz, 1H); 8.47 (d, J=3.7 Hz, 1H) 8.58 (s, 1H); 9.12 (d, J=7.8 Hz, 1H); 9.44 (s, 1H); 10.12 (s, 1H)

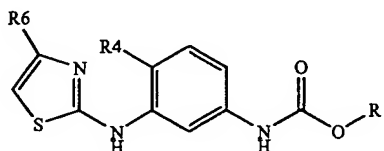
090: N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-morpholin-4-yl-benzamide



beige powder mp: 247-248° C. <sup>1</sup>H RMN (CDCl<sub>3</sub>) δ=1.50 (s, 3H); 3.15-3.18 (m, 4H); 3.79-3.82 (m, 3H); 6.85 (s, 1H); 7.00-7.30 (m, 7H); 7.41 (s, 1H); 7.75 (s, 1H); 8.08 (d, J=7.9 Hz, 1H); 8.22 (d, J=1.7 Hz, 1H); 8.46 (dd, J=1.3 Hz, J=4.7 Hz, 1H); 9.01 (d, J=1.6 Hz, 1H)

Among the compounds of formula II, the invention is particularly embodied by the compounds wherein X is a —OR group, corresponding to the family [3-(Thiazol-2-ylamino)-phenyl]-carbamate and the following formula II-6

FORMULA II-6



wherein R is independently chosen from an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom and/or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with a heteroatom, notably a halogen selected from I, Cl, Br and F and/or bearing a pendant basic nitrogen functionality;

R<sup>4</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>6</sup> is one of the following:

- (i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;
- (ii) a heteroaryl group such as a 2,3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combi-

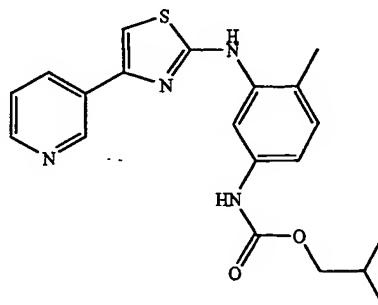
54

nation of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

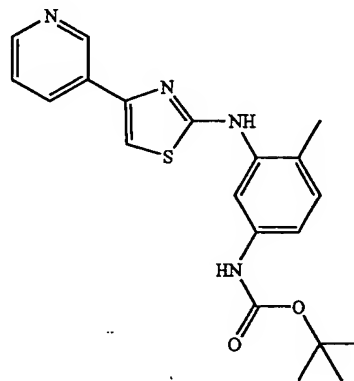
- iv) H, a halogen selected from I, F, Cl or Br, NH<sub>2</sub>, NO<sub>2</sub> or SO<sub>2</sub>-R, wherein R is a linear or branched alkyl group containing one or more group such as 1 to 10 carbon atoms, and optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, and/or bearing a pendant basic nitrogen functionality.

## EXAMPLES

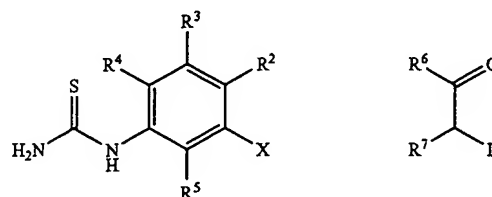
097: [4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-carbamic acid isobutyl ester



098: [4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-carbamic acid tert-butyl ester



In a second embodiment, the invention is directed to a process for manufacturing a compound of formula I depicted above. This entails the condensation of a substrate of general formula 10 with a thiourea of the type 11a-11d.



11 a: X = NH—R<sup>1</sup>

11 b: X = NH<sub>2</sub>

11 c: X = NH—PG

11 d: X = NO<sub>2</sub>

10

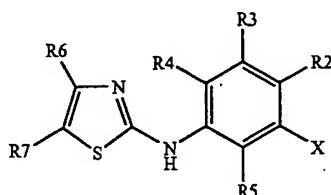
55

Substituent "L" in formula 10 is a leaving group suitable in nucleophilic substitution reactions (for example, L can be selected from chloro, bromo, iodo, toluenesulfonyloxy, methanesulfonyloxy, trifluoromethanesulfonyloxy, etc., with L being preferentially a bromo group).

Group R1 in formula 11a corresponds to group R1 as described in formula I.

Group "PG" in formula 11c is a suitable protecting group of a type commonly utilized by the person skilled in the art.

The reaction of 10 with 1 a-d leads to a thiazole-type product of formula 12a-d.



12 a: X = NH—R1  
12 b: X = NH2  
12 c: X = NH—PG  
12 d: X = NO2

Formula 12a is the same as formula I. Therefore, R1 in 12a corresponds to R1 in formula I.

Formula 12b describes a precursor to compounds of formula I which lack substituent R1. Therefore, in a second phase of the synthesis, substituent R1 is connected to the free amine group in 12b, leading to the complete structure embodied by formula I:

12b+ "R1" → I

The introduction of R1, the nature of which is as described on page 3 for the general formula I, is achieved by the use of standard reactions that are well known to the person skilled in the art, such as alkylation, acylation, sulfonylation, formation of ureas, etc.

Formula 12c describes an N-protected variant of compound 12b. Group "PG" in formula 12c represents a protecting group of the type commonly utilized by the person skilled in the art. Therefore, in a second phase of the synthesis, group PG is cleaved to transform compound 12c into compound 12b. Compound 12b is subsequently advanced to structures of formula I as detailed above.

Formula 12d describes a nitro analogue of compound 12b. In a second phase of the synthesis, the nitro group of compound 12d is reduced by any of the several methods utilized by the person skilled in the art to produce the corresponding amino group, namely compound 12b. Compound 12b thus obtained is subsequently advanced to structures of formula I as detailed above.

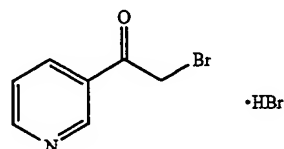
#### Examples of Compound Synthesis

General: All chemicals used were commercial reagent grade products. Dimethylformamide (DMF), methanol (MeOH) were of anhydrous commercial grade and were used without further purification. Dichloromethane and tetrahydrofuran (THF) were freshly distilled under a stream of argon before use. The progress of the reactions was monitored by thin layer chromatography using precoated silica gel 60F 254, Fluka TLC plates, which were visualized under UV light. Multiplicities in <sup>1</sup>H NMR spectra are indicated as singlet (s),

56

broad singlet (br s), doublet (d), triplet (t), quadruplet (q), and multiplet (m) and the NMR spectrum were realized on a 300 MHz Bruker spectrometer.

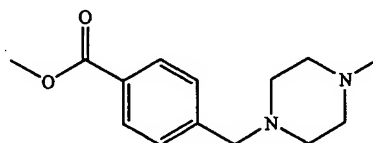
#### 3-Bromoacetyl-pyridine, HBr Salt



Dibromine (17.2 g, 108 mmol) was added dropwise to a cold (0° C.) solution of 3-acetyl-pyridine (12 g, 99 mmol) in acetic acid containing 33% of HBr (165 mL) under vigorous stirring. The vigorously stirred mixture was warmed to 40° C. for 2 h and then to 75° C. After 2 h at 75° C., the mixture was cooled and diluted with ether (400 mL) to precipitate the product, which was recovered by filtration and washed with ether and acetone to give white crystals (100%). This material may be recrystallised from methanol and ether.

IR (neat): 3108, 2047, 2982, 2559, 1709, 1603, 1221, 1035, 798 cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ=5.09 (s, 2H, CH<sub>2</sub>Br); 7.88 (m, 1H, pyridyl-H); 8.63 (m, 1H, pyridyl-H); 8.96 (m, 1H, pyridyl-H); 9.29 (m, 1H, pyridyl-H).

#### Methyl-[4-(1-N-methyl-piperazino)-methyl]-benzoate

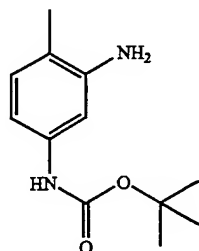


To methyl-4-formyl benzoate (4.92 g, 30 mmol) and N-methyl-piperazine (3.6 mL, 32 mmol) in acetonitrile (100 mL) was added dropwise 2.5 mL of trifluoroacetic acid. The reaction mixture was stirred at room temperature for 1 h. After slow addition of sodium cyanoborohydride (2 g, 32 mmol), the solution was left stirring overnight at room temperature. Water (10 mL) was then added to the mixture, which was further acidified with 1N HCl to pH=6-7. The acetonitrile was removed under reduced pressure and the residual aqueous solution was extracted with diethyl ether (4x30 mL). These extracts were discarded. The aqueous phase was then basified (pH>12) by addition of 2.5N aqueous sodium hydroxide solution. The crude product was extracted with ethyl acetate (4x30 mL). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated under reduced pressure to afford a slightly yellow oil which became colorless after purification by Kugelrohr distillation (190° C.) in 68% yield.

IR (neat): 3322, 2944, 2802, 1721, 1612, 1457, 1281, 1122, 1012 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ=2.27 (s, 3H, NCH<sub>3</sub>); 2.44 (m, 8H, 2xNCH<sub>2</sub>CH<sub>2</sub>N); 3.53 (s, 2H, ArCH<sub>2</sub>N); 3.88 (s, 3H, OCH<sub>3</sub>); 7.40 (d, 2H, J=8.3 Hz, 2xArH); 7.91 (d, 2H, J=8.3 Hz, 2xArH). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ=45.8 (NCH<sub>3</sub>); 51.8 (OCH<sub>3</sub>); 52.9 (2xCH<sub>2</sub>N); 54.9 (2xCH<sub>2</sub>N); 62.4 (ArCH<sub>2</sub>N); 128.7 (2xArC); 129.3 (2xArC); 143.7 (ArC); 166.7 (ArCO<sub>2</sub>CH<sub>3</sub>). MS CI (m/z) (%) 249 (M+1, 100%).

57

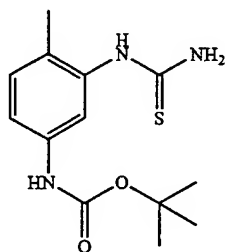
## 2-Methyl-5-tert-butoxycarbonylamino-aniline



A solution of di-tert-butyl dicarbonate (70 g, 320 mmol) in methanol (200 mL) was added over 2 h to a cold ( $-10^{\circ}\text{C}$ .) solution of 2,4-diaminotoluene (30 g, 245 mmol) and triethylamine (30 mL) in methanol (15 mL). The reaction was followed by thin layer chromatography (hexane/ethyl acetate, 3:1) and stopped after 4 h by adding 50 mL of water. The mixture was concentrated in vacuo and the residue was dissolved in 500 mL of ethyl acetate. This organic phase was washed with water (1×150 mL) and brine (2×150 mL), dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure. The resulting light brown solid was washed with small amounts of diethyl ether to give off-white crystals of 2-methyl-5-tert-butoxycarbonylamino-aniline in 67% yield.

IR (neat): 3359; 3246; 2970; 1719; 1609; 1557; 1173; 1050  $\text{cm}^{-1}$ — $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$ =1.50 (s, 9H, tBu); 2.10 (s, 3H,  $\text{ArCH}_3$ ); 3.61 (br s, 2H,  $\text{NH}_2$ ); 6.36 (br s, 1H, NH); 6.51 (dd, 1H,  $J$ =7.9 Hz, 2.3 Hz, ArH); 6.92 (d, 1H,  $J$ =7.9 Hz, ArH); 6.95 (s, 1H, ArH)— $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$ =16.6 ( $\text{ArCH}_3$ ); 28.3 ( $\text{C}(\text{CH}_3)_3$ ); 80.0 ( $\text{C}(\text{CH}_3)_3$ ); 105.2 (ArC); 108.6 (ArC); 116.9 (ArC); 130.4 ( $\text{ArC}-\text{CH}_3$ ); 137.2 ( $\text{ArC}-\text{NH}$ ); 145.0 ( $\text{ArC}-\text{NH}_2$ ); 152.8 ( $\text{COOtBu}$ ) MS ESI ( $m/z$ ) (%): 223 ( $M+1$ ), 167 (55, 100%).

## N-(2-methyl-5-tert-butoxycarbonylamino)phenyl-thiourea



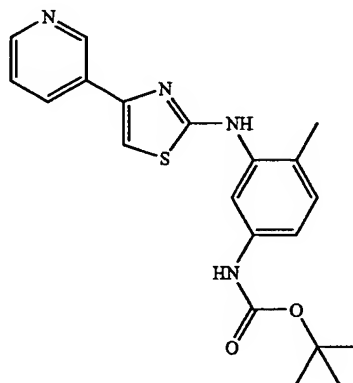
Benzoyl chloride (5.64 g, 80 mmol) was added dropwise to a well-stirred solution of ammonium thiocyanate (3.54 g, 88 mmol) in acetone (50 mL). The mixture was refluxed for 15 min, then, the hydrobromide salt of 2-methyl-5-tert-butoxycarbonylamino-aniline (8.4 g, 80 mmol) was added slowly portionwise. After 1 h, the reaction mixture was poured into ice-water (350 mL) and the bright yellow precipitate was isolated by filtration. This crude solid was then refluxed for 45 min in 70 mL of 2.5 N sodium hydroxide solution. The

58

mixture was cooled down and basified with ammonium hydroxide. The precipitate of crude thiourea was recovered by filtration and dissolved in 150 mL of ethyl acetate. The organic phase was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate, 1:1) to afford 63% of N-(2-methyl-5-tert-butoxycarbonylamino)phenyl-thiourea as a white solid.

IR (neat): 3437, 3292, 3175, 2983, 1724, 1616, 1522, 1161, 1053  $\text{cm}^{-1}$ — $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$ =1.46 (s, 9H, tBu); 2.10 (s, 3H,  $\text{ArCH}_3$ ); 3.60 (br s, 2H,  $\text{NH}_2$ ); 7.10 (d, 1H,  $J$ =8.29 Hz, ArH); 7.25 (d, 1H,  $J$ =2.23 Hz, ArH); 7.28 (d, 1H,  $J$ =2.63 Hz, ArH); 9.20 (s, 1H, ArNH); 9.31 (s, 1H, ArNH)— $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$ =25.1 ( $\text{ArCH}_3$ ); 28.1 ( $\text{C}(\text{CH}_3)_3$ ); 78.9 ( $\text{C}(\text{CH}_3)_3$ ); 16.6 (ArC); 117.5 (ArC); 128.0 (ArC); 130.4 ( $\text{ArC}-\text{CH}_3$ ); 136.5 ( $\text{ArC}-\text{NH}$ ); 137.9 ( $\text{ArC}-\text{NH}$ ); 152.7 ( $\text{COOtBu}$ ); 181.4 ( $\text{C}=\text{S}$ )—MS CI ( $m/z$ ): 282 ( $M+1$ , 100%); 248 (33); 226 (55); 182 (99); 148 (133); 93 (188).

## 2-(2-methyl-5-tert-butoxycarbonylamino)phenyl-4-(3-pyridyl)-thiazole

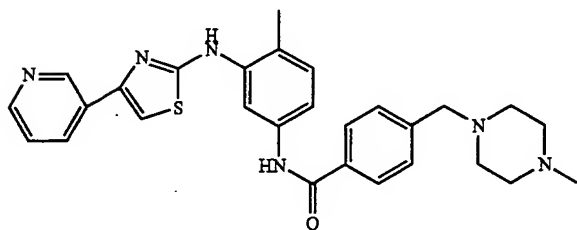


A mixture of 3-bromoacetyl-pyridine, HBr salt (0.81 g, 2.85 mmol), N-(2-methyl-5-tert-butoxycarbonylamino)phenyl-thiourea (0.8 g, 2.85 mmol) and  $\text{KHCO}_3$  ( $\sim 0.4$  g) in ethanol (40 mL) was heated at  $75^{\circ}\text{C}$ . for 20 h. The mixture was cooled, filtered (removal of  $\text{KHCO}_3$ ) and evaporated under reduced pressure. The residue was dissolved in  $\text{CHCl}_3$  (40 mL) and washed with saturated aqueous sodium hydrogen carbonate solution and with water. The organic layer was dried over  $\text{Na}_2\text{SO}_4$  and concentrated. Column chromatographic purification of the residue (hexane/ethyl acetate, 1:1) gave the desired thiazole in 70% yield as an orange solid.

IR (neat): 3380, 2985, 2942, 1748, 1447, 1374, 1239, 1047, 938  $\text{cm}^{-1}$ — $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$ =1.53 (s, 9H, tBu); 2.28 (s, 3H,  $\text{ArCH}_3$ ); 6.65 (s, 1H, thiazole-H); 6.89 (s, 1H); 6.99 (dd, 1H,  $J$ =8.3 Hz, 2.3 Hz); 7.12 (d, 2H,  $J$ =8.3 Hz); 7.35 (dd, 1H,  $J$ =2.6 Hz, 4.9 Hz); 8.03 (s, 1H); 8.19 (dt, 1H,  $J$ =1.9 Hz, 7.9 Hz); 8.54 (br s, 1H, NH); 9.09 (s, 1H, NH)— $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$ =18.02 ( $\text{ArCH}_3$ ); 29.2 ( $\text{C}(\text{CH}_3)_3$ ); 81.3 ( $\text{C}(\text{CH}_3)_3$ ); 104.2 (thiazole-C); 111.6; 115.2; 123.9; 124.3; 131.4; 132.1; 134.4; 139.5; 148.2; 149.1; 149.3; 153.6; 167.3 ( $\text{C}=\text{O}$ )—MS CI ( $m/z$ ) (%): 383 ( $M+1$ , 100%); 339 (43); 327 (55); 309 (73); 283 (99); 71 (311).

59

2-(2-methyl-5-amino)phenyl-4-(3-pyridyl)-thiazole



2-(2-methyl-5-tert-butoxycarbonylamino)phenyl-4-(3-pyridyl)-thiazole (0.40 g, 1.2 mmol) was dissolved in 10 mL of 20% TFA/CH<sub>2</sub>Cl<sub>2</sub>. The solution was stirred at room temperature for 2 h, then it was evaporated under reduced pressure. The residue was dissolved in ethyl acetate. The organic layer was washed with aqueous 1N sodium hydroxide solution, dried over MgSO<sub>4</sub>, and concentrated to afford 2-(2-methyl-5-amino)phenyl-4-(3-pyridyl)-thiazole as a yellow-orange solid in 95% yield. This crude product was used directly in the next step.

A 2M solution of trimethyl aluminium in toluene (2.75 mL) was added dropwise to a cold (0° C.) solution of 2-(2-methyl-5-amino)phenyl-4-(3-pyridyl)-thiazole (0.42 g, 1.5 mmol) in anhydrous dichloromethane (10 mL) under argon atmosphere. The mixture was warmed to room temperature and stirred at room temperature for 30 min. A solution of methyl-4-(1-N-methyl-piperazino)-methyl benzoate (0.45 g, 1.8 mmol) in anhydrous dichloromethane (1 mL) and added slowly, and the resulting mixture was heated at reflux for 5 h. The mixture was cooled to 0° C. and quenched by dropwise addition of a 4N aqueous sodium hydroxide solution (3 mL). The mixture was extracted with dichloromethane (3×20 mL). The combined organic layers were washed with brine (3×20 mL) and dried over anhydrous MgSO<sub>4</sub>. 2-(2-methyl-5-amino)phenyl-4-(3-pyridyl)-thiazole is obtained in 72% after purification by column chromatography (dichloromethane/methanol, 3:1)

IR (neat): 3318, 2926, 1647, 1610, 1535, 1492, 1282, 1207, 1160, 1011, 843—<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ=2.31 (br s, 6H, ArCH<sub>3</sub>+NCH<sub>3</sub>); 2.50 (br s, 8H, 2×NCH<sub>2</sub>CH<sub>2</sub>N); 3.56 (s, 2H, ArCH<sub>2</sub>N); 6.89 (s, 1H, thiazoleH); 7.21-7.38 (m, 4H); 7.45 (m, 2H); 7.85 (d, 2H, J=8.3 Hz); 8.03 (s, 1H); 8.13 (s, 1H); 8.27 (s, 1H); 8.52 (br s, 1H); 9.09 (s, 1H, NH)—<sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 17.8 (ArCH<sub>3</sub>); 46.2 (NCH<sub>3</sub>); 53.3 (NCH<sub>2</sub>); 62.8 (ArCH<sub>2</sub>N); 99.9 (thiazole-C); 112.5; 123.9; 125.2; 127.5; 129.6; 131.6; 133.7; 134.0; 137.6; 139.3; 142.9; 148.8; 149.1; 166.2 (C=O); 166.7 (thiazoleC-NH)—MS CI (m/z) (%): 499 (M+H, 100%); 455 (43); 430 (68); 401 (97); 374 (124); 309 (189); 283 (215); 235 (263); 121 (377); 99 (399).

In a third embodiment, the invention relates to a pharmaceutical composition comprising a compound as depicted above.

Such medicament can take the form of a pharmaceutical composition adapted for oral administration, which can be formulated using pharmaceutically acceptable carriers well known in the art in suitable dosages. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient. In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries which facilitate pro-

60

cessing of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, Pa.).

The composition of the invention can also take the form of a pharmaceutical or cosmetic composition for topical administration.

Such compositions may be presented in the form of a gel, paste, ointment, cream, lotion, liquid suspension aqueous, aqueous-alcoholic or, oily solutions, or dispersions of the lotion or serum type, or anhydrous or lipophilic gels, or emulsions of liquid or semi-solid consistency of the milk type, obtained by dispersing a fatty phase in an aqueous phase or vice versa, or of suspensions or emulsions of soft, semi-solid consistency of the cream or gel type, or alternatively of microemulsions, of microcapsules, of microparticles or of vesicular dispersions to the ionic and/or nonionic type. These compositions are prepared according to standard methods.

The composition according to the invention comprises any ingredient commonly used in dermatology and cosmetic. It may comprise at least one ingredient selected from hydrophilic or lipophilic gelling agents, hydrophilic or lipophilic active agents, preservatives, emollients, viscosity enhancing polymers, humectants, surfactants, preservatives, antioxidants, solvents, and fillers, antioxidants, solvents, perfumes, fillers, screening agents, bactericides, odor absorbers and coloring matter.

As oils which can be used in the invention, mineral oils (liquid paraffin), vegetable oils (liquid fraction of shea butter, sunflower oil), animal oils, synthetic oils, silicone oils (cyclomethicone) and fluorinated oils may be mentioned. Fatty alcohols, fatty acids (stearic acid) and waxes (paraffin, carnauba, beeswax) may also be used as fatty substances.

As emulsifiers which can be used in the invention, glycerol stearate, polysorbate 60 and the PEG-6/PEG-32/glycol stearate mixture are contemplated.

As hydrophilic gelling agents, carboxyvinyl polymers (carbomer), acrylic copolymers such as acrylate/alkylacrylate copolymers, polyacrylamides, polysaccharides such as hydroxypropylcellulose, clays and natural gums may be mentioned, and as lipophilic gelling agents, modified clays such as bentones, metal salts of fatty acids such as aluminum stearates and hydrophobic silica, or alternatively ethylcellulose and polyethylene may be mentioned.

As hydrophilic active agents, proteins or protein hydrolysates, amino acids, polyols, urea, allantoin, sugars and sugar derivatives, vitamins, starch and plant extracts, in particular those of Aloe vera may be used.

As lipophilic active agents, retinol (vitamin A) and its derivatives, tocopherol (vitamin E) and its derivatives, essential fatty acids, ceramides and essential oils may be used. These agents add extra moisturizing or skin softening features when utilized.

In addition, a surfactant can be included in the composition so as to provide deeper penetration of the compound capable of depleting mast cells, such as a tyrosine kinase inhibitor, preferably a c-kit inhibitor.

Among the contemplated ingredients, the invention embraces penetration enhancing agents selected for example from the group consisting of mineral oil, water, ethanol, triacetin, glycerin and propylene glycol; cohesion agents selected for example from the group consisting of polyisobutylene, polyvinyl acetate and polyvinyl alcohol, and thickening agents.

Chemical methods of enhancing topical absorption of drugs are well known in the art.

For example, compounds with penetration enhancing properties include sodium lauryl sulfate (Dugard, P. H. and Sheuplein, R. J., "Effects of Ionic Surfactants on the Permeability of Human Epidermis: An Electrometric Study," *J. Invest. Dermatol.*, V.60, pp. 263-69, 1973), lauryl amine oxide (Johnson et. al., U.S. Pat. No. 4,411,893), azone (Rajadhyaksha, U.S. Pat. Nos. 4,405,616 and 3,989,816) and decylmethyl sulfoxide (Sekura, D. L. and Scala, J., "The Percutaneous Absorption of Alkylmethyl Sulfides," *Pharmacology of the Skin, Advances In Biology of Skin*, (Appleton-Century Craft) V. 12, pp. 257-69, 1972). It has been observed that increasing the polarity of the head group in amphoteric molecules increases their penetration-enhancing properties but at the expense of increasing their skin irritating properties (Cooper, E. R. and Berner, B., "Interaction of Surfactants with Epidermal Tissues: Physicochemical Aspects," *Surfactant Science Series*, V. 16, Reiger, M. M. ed. (Marcel Dekker, Inc.) pp. 195-210, 1987).

A second class of chemical enhancers are generally referred to as co-solvents. These materials are absorbed topically relatively easily, and, by a variety of mechanisms, achieve permeation enhancement for some drugs. Ethanol (Gale et. al., U.S. Pat. No. 4,615,699 and Campbell et. al., U.S. Pat. Nos. 4,460,372 and 4,379,454), dimethyl sulfoxide (U.S. Pat. Nos. 3,740,420 and 3,743,727, and U.S. Pat. No. 4,575,515), and glycerine derivatives (U.S. Pat. No. 4,322,433) are a few examples of compounds which have shown an ability to enhance the absorption of various compounds.

The pharmaceutical compositions of the invention can also be intended for administration with aerosolized formulation to target areas of a patient's respiratory tract.

Devices and methodologies for delivering aerosolized bursts of a formulation of a drug is disclosed in U.S. Pat. No. 5,906,202. Formulations are preferably solutions, e.g. aqueous solutions, ethanoic solutions, aqueous/ethanoic solutions, saline solutions, colloidal suspensions and microcrystalline suspensions. For example aerosolized particles comprise the active ingredient mentioned above and a carrier, (e.g., a pharmaceutically active respiratory drug and carrier) which are formed upon forcing the formulation through a nozzle which nozzle is preferably in the form of a flexible porous membrane. The particles have a size which is sufficiently small such that when the particles are formed they remain suspended in the air for a sufficient amount of time such that the patient can inhale the particles into the patient's lungs.

The invention encompasses the systems described in U.S. Pat. No. 5,556,611:

liquid gas systems (a liquefied gas is used as propellant gas (e.g. low-boiling FCHC or propane, butane) in a pressure container,

suspension aerosol (the active substance particles are suspended in solid form in the liquid propellant phase),

pressurized gas system (a compressed gas such as nitrogen, carbon dioxide, dinitrogen monoxide, air is used.

Thus, according to the invention the pharmaceutical preparation is made in that the active substance is dissolved or dispersed in a suitable nontoxic medium and said solution or dispersion atomized to an aerosol, i.e. distributed extremely finely in a carrier gas. This is technically possible for example in the form of aerosol propellant gas packs, pump aerosols or other devices known per se for liquid misting and solid atomizing which in particular permit an exact individual dosage.

Therefore, the invention is also directed to aerosol devices comprising the compound as defined above and such a formulation, preferably with metered dose valves.

The pharmaceutical compositions of the invention can also be intended for intranasal administration.

In this regard, pharmaceutically acceptable carriers for administering the compound to the nasal mucosal surfaces will be readily appreciated by the ordinary artisan. These carriers are described in the Remington's *Pharmaceutical Sciences* 16th edition, 1980, Ed. By Arthur Osol, the disclosure of which is incorporated herein by reference.

The selection of appropriate carriers depends upon the particular type of administration that is contemplated. For administration via the upper respiratory tract, the composition can be formulated into a solution, e.g., water or isotonic saline, buffered or unbuffered, or as a suspension, for intranasal administration as drops or as a spray. Preferably, such solutions or suspensions are isotonic relative to nasal secretions and of about the same pH, ranging e.g., from about pH 4.0 to about pH 7.4 or, from pH 6.0 to pH 7.0. Buffers should be physiologically compatible and include, simply by way of example, phosphate buffers. For example, a representative nasal decongestant is described as being buffered to a pH of about 6.2 (Remington's, Id. at page 1445). Of course, the ordinary artisan can readily determine a suitable saline content and pH for an innocuous aqueous carrier for nasal and/or upper respiratory administration.

Common intranasal carriers include nasal gels, creams, pastes or ointments with a viscosity of, e.g., from about 10 to about 3000 cps, or from about 2500 to 6500 cps, or greater, may also be used to provide a more sustained contact with the nasal mucosal surfaces. Such carrier viscous formulations may be based upon, simply by way of example, alkylcelluloses and/or other biocompatible carriers of high viscosity well known to the art (see e.g., Remington's, cited supra. A preferred alkylcellulose is, e.g., methylcellulose in a concentration ranging from about 5 to about 1000 or more mg per 100 ml of carrier. A more preferred concentration of methyl cellulose is, simply by way of example, from about 25 to about mg per 100 ml of carrier.

Other ingredients, such as art known preservatives, colorants, lubricating or viscous mineral or vegetable oils, perfumes, natural or synthetic plant extracts such as aromatic oils, and humectants and viscosity enhancers such as, e.g., glycerol, can also be included to provide additional viscosity, moisture retention and a pleasant texture and odor for the formulation. For nasal administration of solutions or suspensions according to the invention, various devices are available in the art for the generation of drops, droplets and sprays.

A premeasured unit dosage dispenser including a dropper or spray device containing a solution or suspension for delivery as drops or as a spray is prepared containing one or more doses of the drug to be administered and is another object of the invention. The invention also includes a kit containing one or more unit dehydrated doses of the compound, together with any required salts and/or buffer agents, preservatives, colorants and the like, ready for preparation of a solution or suspension by the addition of a suitable amount of water.

Another aspect of the invention is directed to the use of said compound to manufacture a medicament. In other words, the invention embraces a method for treating a disease related to unregulated c-kit transduction comprising administering an effective amount of a compound as defined above to a mammal in need of such treatment.

More particularly, the invention is aimed at a method for treating a disease selected from autoimmune diseases, allergic diseases, bone loss, cancers such as leukemia and GIST, tumor angiogenesis, inflammatory diseases, inflammatory bowel diseases (IBD), interstitial cystitis, mastocytosis, infections diseases, metabolic disorders, fibrosis, diabetes

and CNS disorders comprising administering an effective amount a compound depicted above to a mammal in need of such treatment.

The above described compounds are useful for manufacturing a medicament for the treatment of diseases related to unregulated c-kit transduction, including, but not limited to:

neoplastic diseases such as mastocytosis, canine mastocytoma, human gastrointestinal stromal tumor ("GIST"), small cell lung cancer, non-small cell lung cancer, acute myelocytic leukemia, acute lymphocytic leukemia, myelodysplastic syndrome, chronic myelogenous leukemia, colorectal carcinomas, gastric carcinomas, gastrointestinal stromal tumors, testicular cancers, glioblastomas, solid tumors and astrocytomas.

tumor angiogenesis.

metabolic diseases such as diabetes mellitus and its chronic complications; obesity; diabete type II; hyperlipidemias and dyslipidemias; atherosclerosis; hypertension; and cardiovascular disease.

allergic diseases such as asthma, allergic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, angioedema, atopic dermatitis, allergic contact dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis and insect bite skin inflammation and blood sucking parasitic infestation.

interstitial cystitis.

bone loss (osteoporosis).

inflammatory diseases such as rheumatoid arthritis, conjunctivitis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions.

autoimmune diseases such as multiple sclerosis, psoriasis, intestine inflammatory disease, ulcerative colitis, Crohn's disease, rheumatoid arthritis and polyarthritis, local and systemic scleroderma, systemic lupus erythematosus, discoid lupus erythematosus, cutaneous lupus, dermatomyositis, polymyositis, Sjogren's syndrome, nodular panarthritis, autoimmune enteropathy, as well as proliferative glomerulonephritis.

graft-versus-host disease or graft rejection in any organ transplantation including kidney, pancreas, liver, heart, lung, and bone marrow.

Other autoimmune diseases embraced by the invention active chronic hepatitis and chronic fatigue syndrome subepidermal blistering disorders such as pemphigus.

Vasculitis.

melanocyte dysfunction associated diseases such as hypermelanosis resulting from melanocyte dysfunction and including lentigines, solar and senile lentigo, Dubreuilh melanosis, moles as well as malignant melanomas. In this regard, the invention embraces the use of the compounds defined above to manufacture a medicament or a cosmetic composition for whitening human skin.

CNS disorders such as psychiatric disorders, migraine, pain, memory loss and nerve cells degeneracy. More particularly, the method according to the invention is useful for the treatment of the following disorders: Depression including dysthymic disorder, cyclothymic disorder, bipolar depression, severe or "melancholic" depression, a typical depression, refractory depression, seasonal depression, anorexia, bulimia, premenstrual syndrome, post-menopause syndrome, other syndromes such as mental slowing and loss of concentration, pessimistic worry, agitation, self-deprecation, decreased libido, pain including, acute pain, postoperative pain, chronic pain, nociceptive pain, cancer pain, neuropathic pain, psychogenic pain syndromes, anxiety disorders including anxiety associated with hyperventilation and

cardiac arrhythmias, phobic disorders, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, psychiatric emergencies such as panic attacks, including psychosis, delusional disorders, conversion disorders, phobias, mania, delirium, dissociative episodes including dissociative amnesia, dissociative fugue and dissociative identity disorder, depersonalization, catatonia, seizures, severe psychiatric emergencies including suicidal behaviour, self-neglect, violent or aggressive behaviour, trauma, borderline personality, and acute psychosis, schizophrenia including paranoid schizophrenia, disorganized schizophrenia, catatonic schizophrenia, and undifferentiated schizophrenia,

neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, Huntington's disease, the prion diseases, Motor Neurone Disease (MND), and Amyotrophic Lateral Sclerosis (ALS).

substance use disorders as referred herein include but are not limited to drug addiction, drug abuse, drug habituation, drug dependence, withdrawal syndrome and overdose.

Cerebral ischemia

Fibrosis

Duchenne muscular dystrophy

Regarding mastocytosis, the invention contemplates the use of the compounds as defined above for treating the different categories which can be classified as follows:

The category I is composed by two sub-categories (IA and IB). Category IA is made by diseases in which mast cell infiltration is strictly localized to the skin. This category represents the most frequent form of the disease and includes: i) urticaria pigmentosa, the most common form of cutaneous mastocytosis, particularly encountered in children, ii) diffuse cutaneous mastocytosis, iii) solitary mastocytoma and iv) some rare subtypes like bullous, erythrodermic and teleangiectatic mastocytosis. These forms are characterized by their excellent prognosis with spontaneous remissions in children and a very indolent course in adults. Long term survival of this form of disease is generally comparable to that of the normal population and the translation into another form of mastocytosis is rare. Category IB is represented by indolent systemic disease (SM) with or without cutaneous involvement. These forms are much more usual in adults than in children. The course of the disease is often indolent, but sometimes signs of aggressive or malignant mastocytosis can occur, leading to progressive impaired organ function.

The category II includes mastocytosis with an associated hematological disorder, such as a myeloproliferative or myelodysplastic syndrome, or acute leukemia. These malignant mastocytosis does not usually involve the skin. The progression of the disease depends generally on the type of associated hematological disorder that conditions the prognosis.

The category III is represented by aggressive systemic mastocytosis in which massive infiltration of multiple organs by abnormal mast cells is common. In patients who pursue this kind of aggressive clinical course, peripheral blood features suggestive of a myeloproliferative disorder are more prominent. The progression of the disease can be very rapid, similar to acute leukemia, or some patients can show a longer survival time.

Finally, the category IV of mastocytosis includes the mast cell leukemia, characterized by the presence of circulating mast cells and mast cell progenitors representing more than 10% of the white blood cells. This entity represents probably the rarest type of leukemia in humans, and has a very poor

65

prognosis, similar to the rapidly progressing variant of malignant mastocytosis. Mast cell leukemia can occur either de novo or as the terminal phase of urticaria pigmentosa or systemic mastocytosis.

The invention also contemplates the method as depicted for the treatment of recurrent bacterial infections, resurging infections after asymptomatic periods such as bacterial cystitis. More particularly, the invention can be practiced for treating FimH expressing bacteria infections such as Gram-negative enterobacteria including *E. coli*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Citrobacter freundii* and *Salmonella typhimurium*. In this method for treating bacterial infection, separate, sequential or concomitant administration of at least one antibiotic selected bacitracin, the cephalosporins, the penicillins, the aminoglycosides, the tetracyclines, the streptomycins and the macrolide antibiotics such as erythromycin; the fluoroquinolones, actinomycin, the sulfonamides and trimethoprim, is of interest.

In one preferred embodiment, the invention is directed to a method for treating neoplastic diseases such as mastocytosis, canine mastocytoma, human gastrointestinal stromal tumor ("GIST"), small cell lung cancer, non-small cell lung cancer, acute myelocytic leukemia, acute lymphocytic leukemia, myelodysplastic syndrome, chronic myelogenous leukemia, colorectal carcinomas, gastric carcinomas, gastrointestinal stromal tumors, testicular cancers, glioblastomas, and astrocytomas comprising administering a compound as defined herein to a human or mammal, especially dogs and cats, in need of such treatment.

In one other preferred embodiment, the invention is directed to a method for treating allergic diseases such as asthma, allergic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, angioedema, atopic dermatitis, allergic contact dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing vasculitis and insect bite skin inflammation and blood sucking parasitic infestation comprising administering a compound as defined herein to a human or mammal, especially dogs and cats, in need of such treatment.

In still another preferred embodiment, the invention is directed to a method for treating inflammatory diseases such as rheumatoid arthritis, conjunctivitis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions comprising administering a compound as defined herein to a human in need of such treatment.

In still another preferred embodiment, the invention is directed to a method for treating autoimmune diseases such as multiple sclerosis, psoriasis, intestine inflammatory disease, ulcerative colitis, Crohn's disease, rheumatoid arthritis and polyarthritis, local and systemic scleroderma, systemic lupus erythematosus, discoid lupus erythematosus, cutaneous lupus, dermatomyositis, polymyositis, Sjogren's syndrome, nodular panarteritis, autoimmune enteropathy, as well as proliferative glomerulonephritis comprising administering a compound as defined herein to a human in need of such treatment.

In still another preferred embodiment, the invention is directed to a method for treating graft-versus-host disease or graft rejection in any organ transplantation including kidney, pancreas, liver, heart, lung, and bone marrow comprising administering a compound as defined herein to a human in need of such treatment.

66

## Example 1

## In Vitro TK Inhibition Assays

## Procedure

Experiments were performed using purified intracellular domain of c-kit expressed in baculovirus. Estimation of the kinase activity was assessed by the phosphorylation of tyrosine containing target peptide estimated by established ELISA assay.

## Experimental Results on Tested Compounds

Result in Table 1 shows the potent inhibitory action of the catalytic activity of c-kit with an IC<sub>50</sub><10 μM. Further experiments (not shown) indicates that at least one compound acts as perfect competitive inhibitors of ATP.

TABLE 1

Compounds	In vitro Inhibition assay results c-kit IC <sub>50</sub> (μM)
066; 074; 078; 084; 012; 016; 073; 021; 088; 023; 025; 047; 048; 055; 049; 026; 087; 075; 089; 051; 082; 090; 060; 085; 052; 053; 096	<10 μM

## Example 2

## Ex Vivo TK Inhibition Assays

## Procedures

## C-Kit WT and Mutated C-Kit (JM) Assay

## Proliferation Assays

Cells were washed two times in PBS before plating at 5×10<sup>4</sup> cells per well of 96-well plates in triplicate and stimulated either with hematopoietic growth factors (HGF) or without. After 2 days of culture, 37 Bq (1.78 Tbq/mmol) of [<sup>3</sup>H] thymidine (Amersham Life Science, UK) was added for 6 hours. Cells were harvested and filtered through glass fiber filters and [<sup>3</sup>H] thymidine incorporation was measured in a scintillation counter. For proliferation assay, all drugs were prepared as 20 mM stock solutions in DMSO and conserved at -80° C. Fresh dilutions in PBS were made before each experiment. DMSO dissolved drugs were added at the beginning of the culture. Control cultures were done with corresponding DMSO dilutions. Results are represented in percentage by taking the proliferation without inhibitor as 100%.

## Cells

Ba/F3 murine kit and human kit, Ba/F3 mkitΔ27 (juxtamembrane deletion) are derived from the murine IL-3 dependent Ba/F3 proB lymphoid cells. The FMA3 and P815 cell lines are mastocytoma cells expressing endogenous mutated forms of Kit, i.e., frame deletion in the murine juxtamembrane coding region of the receptor-codons 573 to 579. The human leukaemic MC line HMC-1 expresses mutations JM-V560G;

## Immunoprecipitation Assays and Western Blotting Analysis

For each assay, 5.10<sup>6</sup> Ba/F3 cells and Ba/F3-derived cells with various c-kit mutations were lysed and immunoprecipitated as described (Beslu et al., 1996), excepted that cells were stimulated with 250 ng/ml of rmKL. Cell lysates were immunoprecipitated with a rabbit immunserum anti murine KIT, directed against the KIT cytoplasmic domain (Rottapel



67

et al., 1991). Western blot was hybridized either with the 4G10 anti-phosphotyrosine antibody (UBI) or with the rabbit immunoserum anti-murine KIT or with different antibodies (described in antibodies paragraph). The membrane was then incubated either with HRP-conjugated goat anti mouse IgG antibody or with HRP-conjugated goat anti rabbit IgG antibody (Immunotech). Proteins of interest were then visualized by incubation with ECL reagent (Amersham).

#### Experimental Results

The experimental results for various compounds according to the invention using above-described protocols are set forth at Table 2:

TABLE 2

Target	IC50 ( $\mu$ M)	Compounds
c-Kit WT	IC50 <10 $\mu$ M	002; 005; 006; 007; 008; 009; 010; 012; 017; 019; 020; 021; 023; 024; 025; 026; 028; 029; 030; 032; 042; 043; 045; 047; 048; 049; 050; 051; 052; 053; 054; 055; 056; 057; 059; 060; 061; 062; 063; 064; 065; 066; 067; 072; 073; 074; 075; 077; 078; 079; 080; 081; 082; 083; 084; 085; 086; 087; 088; 089; 090; 092; 093; 094; 095; 096; 097; 106; 105; 104; 103; 128; 129; 130; 131; 117; 110; 116; 124; 108; 122; 111; 113; 118; 107;
c-Kit JM A27	IC50 <1 $\mu$ M	028; 074; 029; 009; 012; 073; 020; 042; 061; 065; 088; 025; 048; 049; 050; 089; 051; 082; 090; 083; 059; 052; 053; 066; 103; 067; 104; 078; 079; 105; 081; 084; 030; 010; 021; 043; 054; 062; 106; 023; 024; 064; 047; 055; 026; 087; 075; 085; 005; 077; 092; 060; 032; 017; 063; 093; 094; 095; 086; 093; 096; 108; 117; 122; 008; 080; 111; 118; 113; 007; 072; 019; 056; 057; 107; 097;

#### Example 3

##### In Vivo Activity

##### Procedures

##### GIST

cells: Ba/F3 cells were transfected by c-kit gene having  $\Delta$ 27 mutation (GIST model). Ba/F3 expressing the mutated c-kit gene readily proliferate in the absence of IL3 or SCF and are tumorigenic in nude mice.

##### Protocol:

Mice were irradiated at J-1 (5Gy)  
Tumor cells ( $10^6$ ) were subcutaneously grafted at Jo  
Tumor size were daily measured from J14  
Number of survival mice were daily estimated  
In this experimental model, the tumor size at J14 is about 20 mm<sup>3</sup>

Treated mice received per os twice a day a dose of 100 mg/kg of one compound of formula II-3 during 5 days (from J26 to J30).

##### Rheumatoid Arthritis

The mice were pretreated with the compound of formula II-3 (2 $\times$ , 12.5 mg/kg) for two days (day-2, day-1) before induction of arthritis. Arthritis was induced by ip injection of 150- $\mu$ l serums at days 0 and 2. The treatment with the compound (2 $\times$ , 12.5 mg/kg) was continued for 14 days. The control mice were injected with, 1% PBS before the induction of arthritis and during the course of the disease. Ankle thickness and arthritis score was evaluated for 15 days. Arthritis Score: 5  $\mu$ m of scores of each limb (0 no disease; 1 mild swelling of paw or of just a few digits; 2 clear joint inflammation; 3 severe joint inflammation) maximum score=12. Table 3A and Table 3B show the number of mice used in this

68

study. Two sets of experiments were done with different number of mice, one with 4 mice the other with 8 mice.

TABLE 3A

Treated Mice 2 $\times$ , 12.5 mg/Kg	C57B1/6 6
---	--------------

TABLE 3B

Controls 2X, 1% PBS	C57B1/6 6
------------------------	--------------

##### Histology

At the end of the experiment the hind limbs were collected. The skin of the limb was removed and the limbs were subsequently fixed in 2% Para formaldehyde.

##### Experimental Results

##### GIST

Treated mice (with one compound of formula II-3) displays significant decrease of tumor size at J30 and J33 compared to control.

##### 25 When administrated per os, one tested compound of the formula II-3 displays a significant antitumor activity against tumors cells expressing c-kit A27.

##### RA

A compound of the formula II-3 has demonstrated significant activity in the in vivo mouse model of arthritis. Results are shown on FIGS. 1, 2, 3, 4.

#### BRIEF DESCRIPTION OF DRAWINGS

FIG. 1: Effect of the compound in serum transfer experiments, Protocol, ip daily treatment with the compound (2 $\times$ 12.5 mg/kg) and on days-2 and -1, set of experiment with 4 mice (T: treated, C: control)

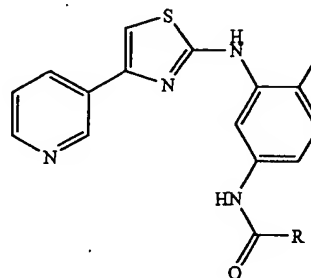
FIG. 2: Effect of the compound in serum transfer experiments, Protocol, ip daily treatment with the compound (2 $\times$ 12.5 mg/kg) and on days-2 and -1, set of experiment with 4 mice (T: treated, C: control)

FIG. 3: Effect of the compound in serum transfer experiments, Protocol, ip daily treatment with the compound (2 $\times$ 12.5 mg/kg) and on days -2 and -1, set of experiment with 8 mice (T: treated, C: control)

FIG. 4: Effect of the compound in serum transfer experiments, Protocol, ip daily treatment with the compound (2 $\times$ 12.5 mg/kg) and on days-2 and -1, set of experiment with 8 mice (T: treated, C: control)

The invention claimed is:

1. A compound according to the following formula:





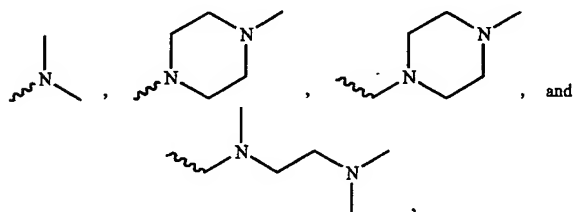
69

wherein R is:

H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality; or

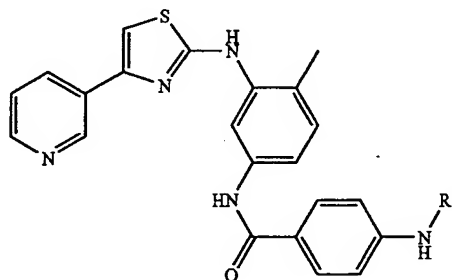
a cycloalkyl, an aryl or heteroaryl group optionally substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

wherein said pendant basic nitrogen functionality is selected from the group consisting of



wherein the wavy line corresponds to the point of attachment.

2. A compound according to the following formula:



wherein R is:

H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality, or

a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one substituent selected from I, Cl, Br, F, and a pendant basic nitrogen functionality; or

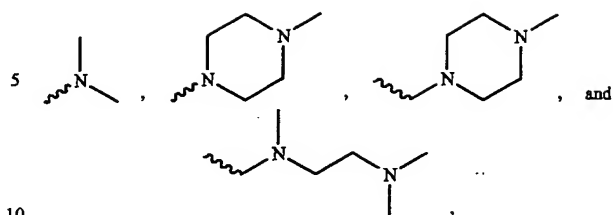
a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one substituent selected from I, Cl, Br, F, and a pendant basic nitrogen functionality; or

a  $\text{—SO}_2\text{—R}''$  group wherein  $\text{R}''$  is an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality; or

a  $\text{—CO—R}'$  or  $\text{—CO—NR}'\text{R}''$  group, wherein  $\text{R}'$  and  $\text{R}''$  are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

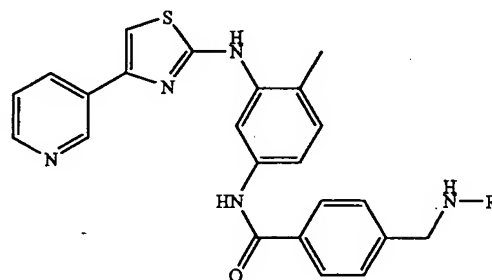
wherein said pendant basic nitrogen functionality is selected from the group consisting of

70



wherein the wavy line corresponds to the point of attachment.

3. A compound according to the following formula:



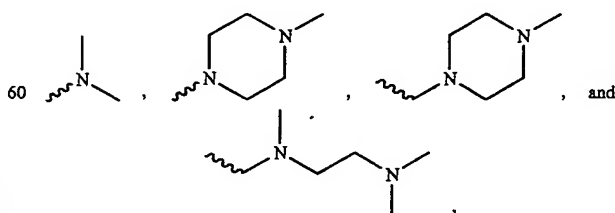
wherein R is H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

a cycloalkyl, aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

an alkyl, cycloalkyl, aryl or heteroaryl group substituted by a alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

a  $\text{—SO}_2\text{—R}''$  group wherein  $\text{R}''$  is an alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

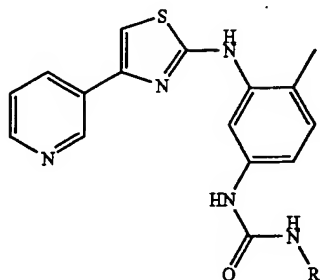
a  $\text{—CO—R}'$  or a  $\text{—CO—NR}'\text{R}''$  group, wherein  $\text{R}'$  and  $\text{R}''$  are independently chosen from H or an aryl heteroaryl, alkyl and cycloalkyl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality; wherein said pendant basic nitrogen functionality is selected from the group consisting of



wherein the wavy line corresponds to the point of attachment.

71

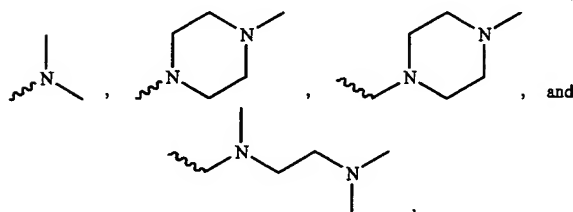
4. A compound according to of the following formula:



wherein R is:

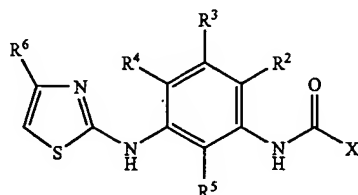
H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

wherein said pendant basic nitrogen functionality is selected from the group consisting of



wherein the wavy line corresponds to the point of attachment.

5. A compound according to formula II:

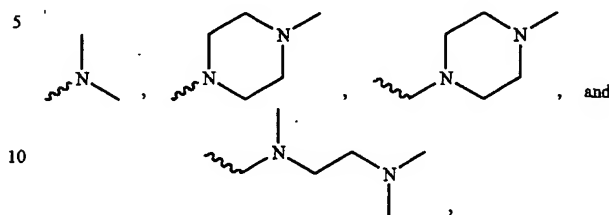


FORMULA II

wherein X is R or NRR' and wherein R and R' are independently chosen from H, an aryl, an heteroaryl, an alkyl and a cycloalkyl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality; an aryl, an heteroaryl, an alkyl and a cycloalkyl group substituted with an aryl, an heteroaryl, an alkyl and a cycloalkyl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

72

wherein said pendant basic nitrogen functionality is selected from the group consisting of



wherein the wavy line corresponds to the point of attachment;

R<sup>2</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>3</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>4</sup> is halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>5</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>6</sup> is one of the following:

- (i) an aryl group optionally substituted by one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, or alkoxy;
- (ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear one or more substituents;
- (iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl, which may additionally bear one or more substituents.

6. A compound according to claim 5 selected from the group consisting of:

1-(4-Bromo-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 010);

1-(4-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 012);

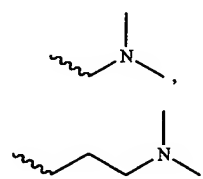
1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-thiophen-2-yl-urea (example 015);

1-(3,5-Dimethyl-isoxazol-4-yl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 019);

1-(2-Iodo-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 020); and

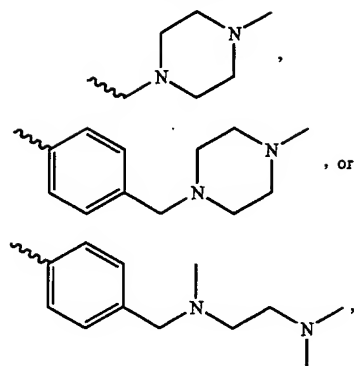
1-(4-Dimethylamino-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 022).

7. A compound according to claim 5, wherein X is selected from the structures (a)-(d) and (f) shown below:



73

-continued



wherein the wavy line corresponds to the point of attachment to core structure of formula II.

8. A compound according to claim 7, wherein X is group (d) and R<sup>6</sup> is a 3-pyridyl group.

9. A compound according to claim 7, wherein X is group (d) and R<sup>4</sup> is a methyl group.

10. A compound according to claim 7, wherein X is group (d) and R<sup>2</sup> and/or R<sup>3</sup> and/or R<sup>5</sup> is H.

11. The compound of claim 5 which is: 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-4-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 080).

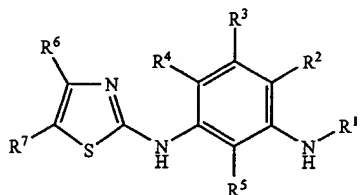
12. A compound which is: N-[3-[4-(4-cyano-phenyl)-thiazol-2-ylamino]]-4-methyl-phenyl-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 081).

13. The compound of claim 5 which is: 4-(4-methyl-piperazin-1-yl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 060) or 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 066).

14. A compound which is: 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 066).

15. A composition comprising a compound of claim 14 and a pharmaceutically acceptable carrier.

16. A compound of formula I:



wherein R<sup>1</sup> is:

—C(O)R, —C(O)OR, or —CO—NRR', wherein R and R' are independently selected from the group consisting of hydrogen, aryl, heteroaryl, alkyl, and cycloalkyl, each optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality;

R<sup>2</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

74

R<sup>3</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>4</sup> is halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>5</sup> is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R<sup>6</sup> is one of the following:

(i) an aryl group such as phenyl optionally substituted by one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, or alkoxy;

(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear one or more substituents; or

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl, which may additionally bear one or more substituents;

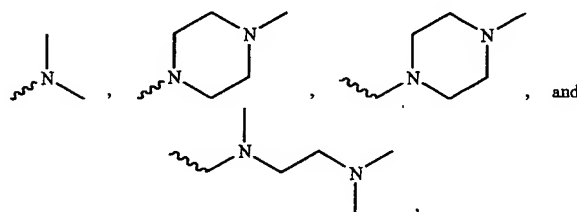
and R<sup>7</sup> is one of the following:

(i) an aryl group such as phenyl optionally substituted by one or more substituents;

(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear one or more substituents;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl, which may additionally bear one or more substituents; or

(iv) H, a halogen selected from I, F, Cl or Br; NH<sub>2</sub>, NO<sub>2</sub> and SO<sub>2</sub>—R", wherein R" is a linear or branched alkyl group optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality; wherein said pendant basic nitrogen functionality is selected from the group consisting of



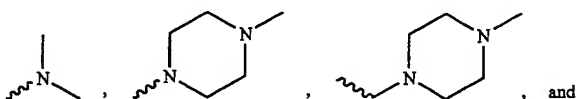
FORMULA I

wherein the wavy line corresponds to the point of attachment.

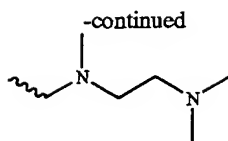
17. A composition comprising a compound of claim 16 in a pharmaceutically acceptable carrier.

18. A compound according to claim 16, wherein R' is

—C(O)R, wherein R is independently selected from the group consisting of hydrogen, aryl, heteroaryl, alkyl, and cycloalkyl, each optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality; wherein said pendant basic nitrogen functionality is selected from the group consisting of



75



wherein the wavy line corresponds to the point of attachment.

19. A compound according to claim 18 selected from the group consisting of:

- N-[4-Methyl-3-(4-phenyl-thiazol-2-ylamino)-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 004);
- N-[3-([2,4']Bithiazolyl-2'-ylamino)-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide; (example 005);
- N-[4-Chloro-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 027);
- 3-Bromo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 028);
- 3-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 029);
- 2-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 032);
- 4-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 033);
- 3-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 045);
- 4-Dimethylamino-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 047);
- 4-(4-Methyl-piperazin-1-yl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylmethyl)-phenyl]-benzamide (example 060);
- N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-isonicotinamide (example 063);
- 2,6-Dichloro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-isonicotinamide (example 064);
- 3,5-Dibromo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 067);
- 3-Fluoro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 074);
- 2,3,5,6-Tetrafluoro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 076);
- N-[3-[4-(4-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 077);
- 3-Bromo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 078);
- 3-Chloro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 079);
- N-[4-Methyl-3-[4-(5-methyl-pyridin-3-yl)-thiazol-2-ylamino]-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 084);
- 3-Iodo-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 085);
- 3-Dimethylamino-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 088);

76

3-(4-Methyl-piperazin-1-yl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 089);

Cyclohexanecarboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide (example 092);

5-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-pentanoic acid ethyl ester (example 093);

4-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 104);

N-[3-[4-(4-Chloro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 108);

N-[3-[4-(4-Methoxy-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 110);

N-[3-[4-(3-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 111);

N-[3-[4-(3-Methoxy-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 113);

4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-[4-(3-trifluoromethyl-phenyl)-thiazol-2-ylamino]-phenyl]-benzamide (example 116);

N-[3-[4-(2-Fluoro-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 118);

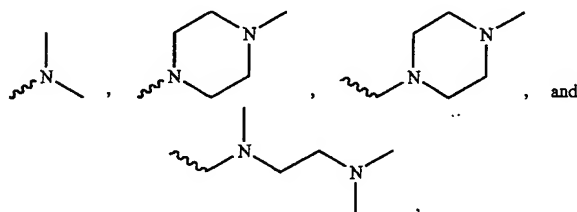
4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-2-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 122); and

N-[3-[4-(2,5-Dimethyl-phenyl)-thiazol-2-ylamino]-4-methyl-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (example 124).

20. A pharmaceutical composition comprising a compound according to claim 18 and a pharmaceutically acceptable carrier.

21. A compound according to claim 16, wherein R' is —CO—NRR', wherein R and R' are independently selected from the group consisting of hydrogen, aryl, heteroaryl, alkyl, and cycloalkyl, each optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality;

wherein said pendant basic nitrogen functionality is selected from the group consisting of



wherein the wavy line corresponds to the point of attachment.

22. A compound according to claim 21 selected from the group consisting of:

1-(2-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 023);

1-(2-Chloro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 024); and

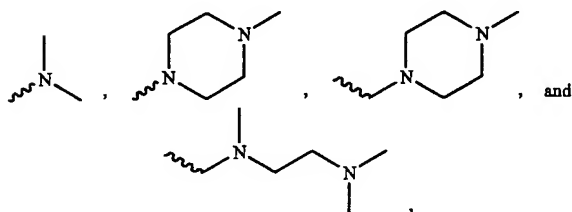
1-(3-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 025).

77

23. A pharmaceutical composition comprising a compound according to claim 21 and a pharmaceutically acceptable carrier.

24. A compound according to claim 16, wherein R' is

—C(O)OR, wherein R is selected from the group consisting of hydrogen, aryl, heteroaryl, alkyl, and cycloalkyl, each optionally substituted with at least one substituent selected from the group consisting of halogen and a pendant basic nitrogen functionality; wherein said pendant basic nitrogen functionality is selected from the group consisting of



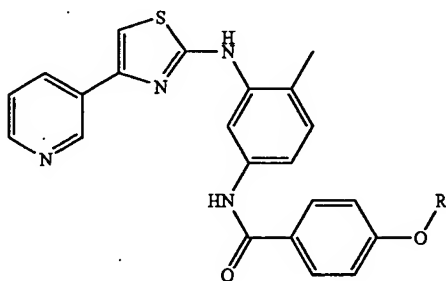
wherein the wavy line corresponds to the point of attachment.

25. A compound according to claim 24 selected from the group consisting of:

[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-carbamic acid isobutyl ester (example 097), and [4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-carbamic acid tert-butyl ester (example 098).

26. A pharmaceutical composition comprising a compound according to claim 25 and a pharmaceutically acceptable carrier.

27. A compound according to the following formula:



wherein R is H or a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom, or bearing at least one pendant basic nitrogen functionality;

a cycloalkyl, aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality; or

an alkyl, cycloalkyl, aryl or heteroaryl group substituted by a alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality; or

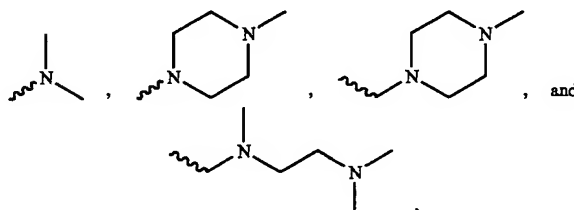
a —SO<sub>2</sub>-R" group wherein R" is an alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

a —CO-R' or a —CO—NR'R"—group wherein R' and R" are independently chosen from H or an aryl het-

78

eroaryl, alkyl and cycloalkyl group optionally substituted with at least one substituent selected from the group consisting of a halogen and a pendant basic nitrogen functionality;

wherein said pendant basic nitrogen functionality is selected from the group consisting of selected from the group consisting of



wherein the wavy line corresponds to the point of attachment.

28. A compound according to claim 27 selected from the group consisting of

4-Hydroxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 037);

Thiophene-2-sulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester (example 042);

4-Iodo-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester (example 043);

4-Isopropoxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 050);

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(2-morpholin-4-yl-ethoxy)-benzamide (example 052);

3-Fluoro-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester (example 056);

2-Fluoro-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester (example 058); and

3-Methoxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 059).

29. A compound according to claim 2 selected from the group consisting of

4-[3-(4-Bromo-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 036);

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-(3-thiophen-2-yl-ureido)-benzamide (example 038);

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-(thiophene-2-sulfonylamino)-benzamide (example 044);

4-[3-(2-Iodo-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 101); and

4-[3-(4-Fluoro-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 102).

30. A compound selected from the group consisting of 1-(4-Methoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 009);

1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(4-trifluoromethyl-phenyl)-urea (example 011);

1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(3,4,5-trimethoxy-phenyl)-urea (example 013);

4-{3-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-ureido}-benzoic acid ethyl ester (example 014);  
 1-Cyclohexyl-1-(N-Cyclohexyl-formamide)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 016);  
 1-(2,4-Dimethoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 017);  
 1-(2-Iodo-phenyl)-1-(N-(2-Iodo-phenyl)-formamide)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 018);  
 1-(4-Difluoromethoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea (example 021);  
 1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-p-tolyl-urea (example 026);  
 (4-Hydroxymethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 030);  
 4-(3-{4-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl}-ureido)-benzoic acid ethyl ester (example 034);  
 N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide (example 035);  
 4-[3-(3,5-Dimethyl-isoxazol-4-yl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 039);  
 4-[3-(4-Methoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 040);  
 4-[3-(4-Difluoromethoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 041);  
 2-Fluoro-5-methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 048);  
 4-tert-Butyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 049);

Benzo [1,3]dioxole-5-carboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide (example 051);  
 3-Cyano-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 054);  
 2-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide (example 055);  
 3-Methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 061);  
 Biphenyl-3-carboxylic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide (example 062);  
 N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide (example 065);  
 {4-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-benzyl}-carbamic acid tert-butyl ester (example 073);  
 3-Fluoro-4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 074);  
 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide (example 075);  
 4-(1-Methoxy-ethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 083);  
 N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[3-(4-trifluoromethyl-phenyl)-ureidomethyl]-benzamide (example 086);  
 4-Cyano-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 103);  
 4-[3-(2,4-Dimethoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 100); and  
 3-Bromo-4-methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide (example 105).

\* \* \* \* \*

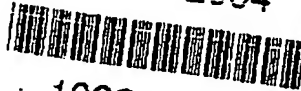
## EXHIBIT B

FORM PTO-1595 (modified)

(Rev. 6-93)

REC'D

01-14-2004



102645416

U.S. DEPARTMENT OF COMMERCE

HEET

Patent and Trademark Office

To the Director of the United States Patent and Trademark Office.

Attached original documents or copies thereof.

## 1. Name of conveying party(ies):

Marco Ciufolini  
Camille Georges Wermuth  
Bruno Marie Gielthen  
Alain Moussy

Additional conveying party(ies) NO

## 2. Name and address of receiving party(ies):

AB Science  
3, Avenue Georges V  
Paris  
75008  
France

2004 JAN 12 AM 8:57  
OPR/FINANCE

## 3. Nature of conveyance:

ASSIGNMENTS

Execution Dates:

10/29/03

Additional name(s) &amp; address(es) attached? NO

## 4. Application number(s) or patent number(s):

If this is being filed together with a new application, the execution date of the application is:

A. Patent Application Number(s):

10/632,101

B. Patent Number(s):

PATENT\_NO

Additional numbers attached? NO

## 5. Name and address of party to whom correspondence concerning document should be mailed:

David P. Lentini  
FOLEY & LARDNER  
One Maritime Plaza  
Sixth Floor  
San Francisco, California 94111-3404

## 6. Total number of applications/patents involved: 1

## 7. Total fee (37 C.F.R. § 3.41): \$40.00

☒ Check Enclosed

Charge to deposit account

## 8. Deposit account number: 19-0741

DO NOT USE THIS SPACE

## 9. Statement and signature:

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document. The Commissioner is hereby authorized to charge any additional recordation fees which may be required in this matter to the above-identified deposit account.

David P. Lentini

1/8/04

Name of person signing

Signature

Date

Total number of pages including cover sheet, attachments, and document: 7

01/13/2004 DBYRNE 00000064 10632101

01 FC:8021

40.00 OP

016.319569.1

PATENT  
REEL: 014872 FRAME: 0028



**ASSIGNMENT**

*For good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, each undersigned inventor has sold and assigned, and by these presents hereby sells and assigns, unto*

name and      **AB SCIENCE**  
address of    **3, Avenue Georges V**  
assignee      **Paris, France 75008**

*(hereinafter ASSIGNEE) all right, title and interest for the United States, its territories and possessions in and to this invention relating to*

*title of invention*

**2-(3-aminoaryl)amino-4-aryl-thiazoles for the treatment of diseases**  
*as set forth in this United States Patent Application*

*check one*      ☐ *executed concurrently herewith*

☐ *executed on*

☒ *Serial No.*    **10/632,101**      *Filed*    **AUGUST 1, 2003**

*in and to said United States Patent Application including any and all divisions or continuations thereof and in and to any and all Letters Patent of the United States which may issue on any such application or for said invention, including any and all reissues or extensions thereof, to be held and enjoyed by said ASSIGNEE, its successors, legal representatives and assigns to the full end of the term or terms for which any and all such Letters Patent may be granted as fully and entirely as would have been held and enjoyed by the undersigned had this Assignment not been made;*

*Each of the undersigned hereby authorizes and requests the Commissioner of Patents and Trademarks to issue any and all such Letters Patent to said ASSIGNEE, its successors or assigns in accordance herewith;*

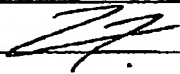
*Each of the undersigned warrants and covenants that he has the full and unencumbered right to sell and assign the interests herein sold and assigned and that he has not executed and will not execute any document or instrument in conflict herewith;*

*Each of the undersigned further covenants and agrees he will communicate to said ASSIGNEE, its successors, legal representatives or assigns all information known to him relating to said invention or patent application and that he will execute and deliver any papers, make all rightful oaths, testify in any legal proceedings and perform all other lawful acts deemed necessary or desirable by said ASSIGNEE, its successors, legal representatives or assigns to perfect title to said invention, to said application including divisions and continuations thereof and to any and all Letters Patent which may be granted therefor or thereon, including reissues or extensions, in said ASSIGNEE, its successors, or assigns or to assist said ASSIGNEE, its successors, legal representatives or assigns in obtaining, reissuing or enforcing Letters Patent of the United States for said invention;*

*Each of the undersigned hereby assigns all right title and interest to this invention to said ASSIGNEE for patent applications in any country claiming benefit of the priority of the present United States application.*

# ASSIGNMENT

Each of the undersigned hereby authorizes the firm of **FOLEY & LARDNER** to insert in this Assignment any further identification which may be necessary or desirable to comply with the rules of the U.S. Patent and Trademark Office for recordation of this Assignment.

<b>NAMES AND SIGNATURES OF INVENTORS</b>		
Name: <b>Marco CIUFOLINI</b>	Signature:	Date:
Name: <b>Camille WERMUTH</b>	Signature:	Date:
Name: <b>Bruno GIELTHEN</b>	Signature:	Date:
Name: <b>Alain MOUSSY</b>	Signature 	Date: <b>10/29/03</b>
<b>NAMES AND SIGNATURES OF WITNESSES</b>		
Name:	Signature:	Date:
Name:	Signature:	Date:
Name:	Signature:	Date:
Name:	Signature:	Date:

Note: Prima facie evidence of execution may optionally be obtained by execution of this document before a U.S. Consul or before a local officer authorized to administer oaths whose authority is proved by a certificate from a U.S. Consul.

# ASSIGNMENT

For good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, each undersigned inventor has sold and assigned, and by these presents hereby sells and assigns, unto

name and AB SCIENCE  
address of 3, Avenue Georges V  
assignee Paris, France 75008

(hereinafter ASSIGNEE) all right, title and interest for the United States, its territories and possessions in and to this invention relating to

title of invention  
2-(3-aminoaryl)amino-4-aryl-thiazoles for the treatment of diseases  
as set forth in this United States Patent Application

check one ☐ executed concurrently herewith  
☐ executed on \_\_\_\_\_  
☒ Serial No. 10/632,101 Filed AUGUST 1, 2003

in and to said United States Patent Application including any and all divisions or continuations thereof and in and to any and all Letters Patent of the United States which may issue on any such application or for said invention, including any and all reissues or extensions thereof, to be held and enjoyed by said ASSIGNEE, its successors, legal representatives and assigns to the full end of the term or terms for which any and all such Letters Patent may be granted as fully and entirely as would have been held and enjoyed by the undersigned had this Assignment not been made;

Each of the undersigned hereby authorizes and requests the Commissioner of Patents and Trademarks to issue any and all such Letters Patent to said ASSIGNEE, its successors or assigns in accordance herewith;

Each of the undersigned warrants and covenants that he has the full and unencumbered right to sell and assign the interests herein sold and assigned and that he has not executed and will not execute any document or instrument in conflict herewith;

Each of the undersigned further covenants and agrees he will communicate to said ASSIGNEE, its successors, legal representatives or assigns all information known to him relating to said invention or patent application and that he will execute and deliver any papers, make all rightful oaths, testify in any legal proceedings and perform all other lawful acts deemed necessary or desirable by said ASSIGNEE, its successors, legal representatives or assigns to perfect title to said invention, to said application including divisions and continuations thereof and to any and all Letters Patent which may be granted therefor or thereon, including reissues or extensions, in said ASSIGNEE, its successors, or assigns or to assist said ASSIGNEE, its successors, legal representatives or assigns in obtaining, reissuing or enforcing Letters Patent of the United States for said invention;

Each of the undersigned hereby assigns all right title and interest to this invention to said ASSIGNEE for patent applications in any country claiming benefit of the priority of the present United States application.

# ASSIGNMENT

Each of the undersigned hereby authorizes the firm of **FOLEY & LARDNER** to insert in this Assignment any further identification which may be necessary or desirable to comply with the rules of the U.S. Patent and Trademark Office for recordation of this Assignment.

NAMES AND SIGNATURES OF INVENTORS		
Name: Marco CIUFOLINI	Signature:	Date:
Name: Camille WERMUTH	Signature: C.G.W. - It.	Date: 10/29/03
Name: Bruno GIELTHEN	Signature: [Signature]	Date: 10/29/03
Name: Alain MOUSSY	Signature:	Date:
NAMES AND SIGNATURES OF WITNESSES		
Name:	Signature:	Date:
Name:	Signature:	Date:
Name:	Signature:	Date:
Name:	Signature:	Date:

Note: Prima facie evidence of execution may optionally be obtained by execution of this document before a U.S. Consul or before a local officer authorized to administer oaths whose authority is proved by a certificate from a U.S. Consul.

**ASSIGNMENT**

*For good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, each undersigned inventor has sold and assigned, and by these presents hereby sells and assigns, unto*

name and **AB SCIENCE**  
 address of **3, Avenue Georges V**  
 assignee **Paris, France 75008**

*(hereinafter ASSIGNEE) all right, title and interest for the United States, its territories and possessions in and to this invention relating to*

*title of invention*  
**2-(3-aminoaryl)amino-4-aryl-thiazoles for the treatment of diseases**  
*as set forth in this United States Patent Application*

check one ☐ executed concurrently herewith  
☐ executed on \_\_\_\_\_  
☒ Serial No. 10/632,101 Filed AUGUST 1, 2003

*in and to said United States Patent Application including any and all divisions or continuations thereof and in and to any and all Letters Patent of the United States which may issue on any such application or for said invention, including any and all reissues or extensions thereof, to be held and enjoyed by said ASSIGNEE, its successors, legal representatives and assigns to the full end of the term or terms for which any and all such Letters Patent may be granted as fully and entirely as would have been held and enjoyed by the undersigned had this Assignment not been made;*

*Each of the undersigned hereby authorizes and requests the Commissioner of Patents and Trademarks to issue any and all such Letters Patent to said ASSIGNEE, its successors or assigns in accordance herewith;*

*Each of the undersigned warrants and covenants that he has the full and unencumbered right to sell and assign the interests herein sold and assigned and that he has not executed and will not execute any document or instrument in conflict herewith;*

*Each of the undersigned further covenants and agrees he will communicate to said ASSIGNEE, its successors, legal representatives or assigns all information known to him relating to said invention or patent application and that he will execute and deliver any papers, make all rightful oaths, testify in any legal proceedings and perform all other lawful acts deemed necessary or desirable by said ASSIGNEE, its successors, legal representatives or assigns to perfect title to said invention, to said application including divisions and continuations thereof and to any and all Letters Patent which may be granted therefor or thereon, including reissues or extensions, in said ASSIGNEE, its successors, or assigns or to assist said ASSIGNEE, its successors, legal representatives or assigns in obtaining, reissuing or enforcing Letters Patent of the United States for said invention;*

*Each of the undersigned hereby assigns all right title and interest to this invention to said ASSIGNEE for patent applications in any country claiming benefit of the priority of the present United States application.*

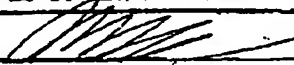
-1-

**PATENT**

**REEL: 014872 FRAME: 0033**

# ASSIGNMENT

Each of the undersigned hereby authorizes the firm of **FOLEY & LARDNER** to insert in this Assignment any further identification which may be necessary or desirable to comply with the rules of the U.S. Patent and Trademark Office for recordation of this Assignment.

NAMES AND SIGNATURES OF INVENTORS		
Name: Marco CIUFOLINI	Signature: 	Date: 10/23/2003
Name: Camille WERMUTH	Signature:	Date:
Name: Bruno GIELTHEN	Signature:	Date:
Name: Alain MOUSSY	Signature:	Date:
NAMES AND SIGNATURES OF WITNESSES		
Name:	Signature:	Date:
Name:	Signature:	Date:
Name:	Signature:	Date:
Name:	Signature:	Date:

Note: Prima facie evidence of execution may optionally be obtained by execution of this document before a U.S. Consul or before a local officer authorized to administer oaths whose authority is proved by a certificate from a U.S. Consul.

## EXHIBIT C

**KINAVET-CA1**  
(masitinib mesylate)  
Tablet  
Antineoplastic

For oral use in dogs only

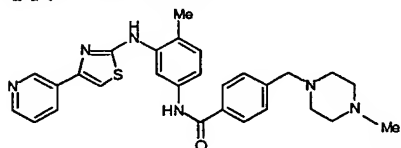
Conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-308.

**CAUTION:**

Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Use only as directed. It is a violation of Federal law to use this product other than as directed in the labeling.

**DESCRIPTION:**

Masitinib is a tyrosine kinase inhibitor. The molecular weight of masitinib base is 498.67. The empirical formula is  $C_{22}H_{20}N_4O_6S$ . The structural formula is:



KINAVET-CA1 tablets are round, biconvex, orange, coated tablets, containing either 50 mg or 150 mg masitinib base as masitinib mesylate. Each tablet is engraved with logo on one side and dosage strength on the other side.

**INDICATIONS:**

KINAVET-CA1 tablets are indicated for the treatment of recurrent (post-surgery) or nonresectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and/or chemotherapy except corticosteroids.

**DOSAGE AND ADMINISTRATION:**

Always provide Client Information Sheet with prescription.

Administer KINAVET-CA1 at an initial dose of 12.5 mg/kg/day (5.7 mg/lb/day) orally, once daily with food (see Table 1). Dose reductions to 9 mg/kg/day (4.1 mg/lb/day, see Table 2) and dose interruptions may be utilized, if needed, to manage adverse reactions (see Table 3 as well as WARNINGS and PRECAUTIONS). Do not split or crush tablets.

Table 1. Initial Dose, 12.5 mg/kg/day Dose Chart

Dog Body Weight		Dose	Number of Tablets	
Pounds	Kilograms		50 mg	150 mg
15.4 - 22.9	7.0 - 10.4	100 mg	2	
23.0 - 30.6	10.5 - 13.9	150 mg		1
30.7 - 39.4	14.0 - 17.9	200 mg	1	1
39.5 - 48.2	18.0 - 21.9	250mg	2	1
48.3 - 57.0	22.0 - 25.9	300 mg		2
57.1 - 65.8	26.0 - 29.9	350 mg	1	2
65.9 - 74.6	30.0 - 33.9	400 mg	2	2
74.7 - 83.4	34.0 - 37.9	450 mg		3
83.5 - 92.2	38.0 - 41.9	500 mg	1	3
92.3 - 101.0	42.0 - 45.9	550 mg	2	3
101.1 - 110.2	46.0 - 49.9	600 mg		4
110.3 - 118.6	50.0 - 53.9	650 mg	1	4
118.7 - 127.4	54.0 - 57.9	700 mg	2	4
127.5 - 136.2	58.0 - 61.9	750 mg		5
136.3 - 145.0	62.0 - 65.9	800 mg	1	5
145.1 - 153.8	66.0 - 69.9	850 mg	2	5
153.9 - 162.6	70.0 - 73.9	900 mg		6
162.7 - 171.4	74.0 - 77.9	950 mg	1	6
171.5 - 220	78.0 - 100.0	1000 mg	2	6

\*KINAVET-CA1 cannot be safely dosed at the target dose of 12.5 mg/kg in dogs weighing less than 7.0 kg (15.4 lbs)

Table 2. Reduced Dose, 9 mg/kg/day Dose Chart

Dog Body Weight		Dose	Number of Tablets	
Pounds	Kilograms		50 mg	150 mg
15.4 - 22.9	7.0 - 10.4	Discontinue treatment*		
23.0 - 31.7	10.5 - 14.4	100 mg	2	
31.8 - 42.7	14.5 - 19.4	150 mg		1
42.8 - 54.8	19.5 - 24.9	200 mg	1	1
54.9 - 67.1	25.0 - 30.5	250mg	2	1
67.2 - 79.4	30.6 - 36.1	300 mg		2
79.5 - 91.5	36.2 - 41.6	350 mg	1	2
91.6 - 103.8	41.7 - 47.2	400 mg	2	2
103.9 - 115.9	47.3 - 52.7	450 mg		3
116.0 - 128.3	52.8 - 58.3	500 mg	1	3
128.4 - 140.4	58.4 - 63.8	550 mg	2	3
140.5 - 152.7	64.0 - 69.4	600 mg		4
152.8 - 164.8	69.5 - 74.9	650 mg	1	4
164.9 - 177.1	75.0 - 80.5	700 mg	2	4
177.1 - 220	80.6 - 100.0	750 mg		5

\*KINAVET-CA1 cannot be effectively dosed at 9 mg/kg in dogs weighing less than 10.5 kg (23.0 lbs)

Table 3. Managing Adverse Reactions with Dose Interruption or Reduction

Toxicity	Dose Adjustment
<b>Renal Toxicities and Protein Loss Syndrome</b>	
Hypoalbuminemia (serum albumin < 0.75X ULN) Proteinuria (UPC > 1) Azotemia (BUN or Creatinine > 1.5X ULN)	If the current dose is 12.5 mg/kg, discontinue treatment until resolution, then resume treatment at 9 mg/kg. If the current dose is 9 mg/kg then permanently discontinue treatment.
<b>Non-Regenerative Anemia and Hemolytic Anemia</b>	
Hematocrit < 30% Hemoglobin < 10 g/dL	Permanently discontinue treatment.
<b>Neutropenia</b>	
Neutrophils < 1500/ $\mu$ L	If the current dose is 12.5 mg/kg, discontinue treatment until resolution, then resume treatment at 9 mg/kg. If the current dose is 9 mg/kg, permanently discontinue treatment.
<b>Hepatic Toxicity</b>	
ALT or AST > 3X ULN Bilirubin > 1.5X ULN	If the current dose is 12.5 mg/kg, discontinue treatment until resolution, then resume treatment at 9 mg/kg. If the current dose is 9 mg/kg, permanently discontinue treatment.
<b>Gastrointestinal Toxicity</b>	
Vomiting and Diarrhea Grade 3 or greater <sup>a</sup>	If the current dose is 12.5 mg/kg, discontinue treatment until resolution, then resume treatment at 9 mg/kg. If the current dose is 9 mg/kg, permanently discontinue treatment.
<b>Other Adverse Reactions</b>	
Severe Weight Loss	Permanently discontinue treatment.

\*LLN = lower limit of normal

<sup>b</sup>ULN = upper limit of normal

<sup>a</sup>Grade 3 diarrhea is an increase of > 6 stools per day over baseline. Grade 3 vomiting is > 5 vomiting episodes in 24 hours, or vomiting for > 4 days.<sup>1</sup>

**CONTRAINDICATIONS:**

Do not initiate KINAVET-CA1 tablet treatment in dogs with:

- Hypoalbuminemia (serum albumin < 1X LLN)
- Proteinuria (urine protein to creatinine [UPC] ratio > 1)
- Azotemia (elevated blood urea nitrogen or creatinine > 1 ULN)
- Anemia (hematocrit < 30% or hemoglobin < 10 g/dL)
- Neutropenia (< 2000/ $\mu$ L)
- AST or ALT elevations (> 3X ULN)
- Hyperbilirubinemia (> 1.5X ULN)

Do not use in dogs that are pregnant, lactating, or intended for breeding. Masitinib caused impaired fertility, fetal resorptions and abnormal development (delayed ossification) in rats.

Do not use in dogs that have a hypersensitivity to masitinib.

**WARNINGS:**

Masitinib was associated with life-threatening or fatal hypoalbuminemia and anemia in field studies and the 39-week safety study. The studies provide evidence that severe adverse reactions may be prevented if dogs are monitored for hypoalbuminemia every 2 weeks and for anemia every 4 weeks, and treatment is discontinued if hypoalbuminemia, proteinuria or anemia occur (see Table 3 and ANIMAL SAFETY).

**HUMAN WARNINGS:**

NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN. Children should not come into contact with KINAVET-CA1. Keep children away from feces, urine, or vomit of treated dogs.

To avoid exposure to drug, wash hands with soap and water after administering KINAVET-CA1 and wear protective gloves to prevent contact with feces, urine, vomit, and broken or crushed KINAVET-CA1 tablets. Place all waste material in a plastic bag and seal before general disposal. If eyes are accidentally exposed to the drug, rinse eyes with water immediately. In case of accidental ingestion by a person, seek medical advice immediately, show the package insert or label to the physician.

Pregnant women, women who may become pregnant, or nursing mothers should pay special attention to these handling precautions (see handling instructions above). KINAVET-CA1 may harm an unborn baby (cause birth defects). For pregnant and nursing women, accidental ingestion of KINAVET-CA1 may have adverse effects on pregnancy or the nursing baby.



## PRECAUTIONS:

Dogs on KINAVET-CA1 tablets should be monitored as follows:

<b>Every 2 weeks:</b>	Hypoalbuminemia Proteinuria
<b>Every 4 weeks:</b>	Azotemia Anemia Neutropenia Elevated AST or ALT Hyperbilirubinemia

In case of a positive semi-quantitative test for proteinuria (dipstick protein  $\geq 30$  mg/dL) or clinical signs of anemia or hemolysis, urine protein should be confirmed with a quantitative test (UPC ratio) and the dog should be tested for hypoalbuminemia, anemia, and azotemia.

Refer to Table 3 under DOSAGE AND ADMINISTRATION for management of adverse reactions.

The safe use of KINAVET-CA1 tablets has not been evaluated in dogs younger than 2 years of age. KINAVET-CA1 cannot be safely dosed in dogs weighing less than 7 kg (15.4 lbs).

KINAVET-CA1 is metabolized in the liver. The influence of concomitant drugs that may inhibit metabolism of KINAVET-CA1 tablets has not been evaluated in dogs. Drug compatibility should be assessed for dogs requiring concomitant therapy. Concomitant treatment with drugs which are metabolized by CYP450 isoenzymes (3A4, 3A5, 2C9, 2D6) may result in higher or lower plasma levels of either KINAVET-CA1 or those drugs, and should be used with caution (see CLINICAL PHARMACOLOGY).

The concomitant use of potentially nephrotoxic drugs and KINAVET-CA1 has not been evaluated.

Vascular homeostasis in dogs taking KINAVET-CA1 that require surgery has not been evaluated.

## ADVERSE REACTIONS:

Adverse reactions associated with KINAVET-CA1 treatment include:

<b>General:</b>	lethargy, weakness, dehydration, behavioral changes, death
<b>Gastrointestinal:</b>	vomiting, diarrhea, bloody stools, melena, constipation, decreased appetite, anorexia
<b>Renal:</b>	azotemia, proteinuria, elevated UPC, polyuria, polydipsia, hemoglobinuria, hematuria, nephrotic/protein loss syndrome
<b>Hepatic:</b>	elevated liver enzymes, elevated bilirubin, ascites, icterus
<b>Cardiorespiratory:</b>	cough, pleural effusion, possible pulmonary thromboembolism, dyspnea, hypertension, tachycardia, cardiomegaly, syncope, circulatory collapse, aspiration pneumonia
<b>Metabolic:</b>	pancreatitis, weight loss, tumor lysis syndrome, mast cell degranulation, periodic hypoglycemia
<b>Hematologic:</b>	anemia, hemolytic anemia, non-regenerative anemia, leukopenia, neutropenia, lymphopenia, thrombocytopenia
<b>Ocular:</b>	hyphema
<b>Skin:</b>	alopecia, increased incidence of lipomas, subcutaneous edema, pruritis
<b>Other:</b>	lymphadenopathy, hemoabdomen, back pain

Refer to Table 3, under DOSAGE AND ADMINISTRATION for management of adverse reactions.

For a copy of the Material Safety Data Sheet (MSDS) or to report adverse reactions, contact AB Science, USA at 973-218-2436 or contact@ab-science.com.

## INFORMATION FOR DOG OWNER:

The dog owner or person responsible for administering KINAVET-CA1 to the dog should receive and read the Client Information Sheet, which describes how to safely administer KINAVET-CA1, monitor for possible adverse reactions and clean up any urine, feces or vomit from dogs treated with KINAVET-CA1. The Client Information Sheet also contains warnings for humans and what to do in case of accidental human exposure to KINAVET-CA1.

## CLINICAL PHARMACOLOGY:

Masitinib is a protein-tyrosine kinase inhibitor. Protein tyrosine kinases are thought to be activated in cancer cells and to drive tumor progression. Tyrosine kinase inhibitor drugs act by interfering with these cell communications and may prevent tumor growth. *In vitro*, masitinib selectively inhibits the mutated form of the c-Kit receptor (a receptor tyrosine kinase) in the juxtamembrane region and the c-Kit wild-type receptor. It also inhibits the platelet-derived growth factor receptor and the fibroblast growth factor receptor 3.

Following oral administration of  $11.2 \pm 0.5$  mg/kg masitinib, as KINAVET-CA1 tablets, in dogs, masitinib was rapidly absorbed reaching a mean ( $\pm$  SD) peak plasma concentration of  $895 (\pm 283)$  ng/mL at  $2.29 (\pm 0.83)$  hours. The mean area under the plasma concentration time-curve (AUC 0-24) was  $5.70 (\pm 1.93)$   $\mu\text{g} \times \text{hr/mL}$ . The mean elimination half-life ( $t_{1/2}$ ) is  $3.24 (\pm 0.42)$  hours. Following administration of KINAVET-CA1 tablets, the fed  $C_{\text{max}}$  was 136% (90% Confidence Limits: 98 – 190%) and the fed AUC was 114% (52 – 252%) of the fasted  $C_{\text{max}}$  and AUC, respectively.

The plasma total body clearance and volume of distribution of masitinib in normal healthy Beagle dogs is approximately 14 mL/min/kg and 17 L/kg, respectively. Masitinib is approximately 90% bound to plasma proteins. Minimal accumulation occurs when masitinib is administered daily at a dose of 12.5 mg/kg. Based on masitinib plasma concentrations at clinically relevant doses in toxicity studies, the inter-animal coefficient of variation in AUC (representing bioavailability) is expected to be about 25%.

Masitinib is metabolized predominantly by N-dealkylation. Elimination is principally in the bile and gastrointestinal tract. *In vitro* testing with human liver microsomes demonstrated that masitinib inhibits the activity of cytochrome P450 isoenzymes CYP2C9, 2D6, 3A4 and 3A5. Results of *in vitro* testing with human hepatocytes were inconsistent; therefore, the potential for masitinib to induce the activity of cytochrome P450 isoenzymes is unclear.

## EFFECTIVENESS:

### Reasonable Expectation of Effectiveness

Effectiveness has not been demonstrated for KINAVET-CA1. A reasonable expectation of effectiveness for conditional approval was based on time to progression (TTP) in a subpopulation of dogs in the following study.

A randomized, placebo controlled, double masked, multi-center field study was conducted to evaluate the safety and effectiveness of KINAVET-CA1 in dogs with Grade II or III cutaneous mast cell tumors recurrent after surgery or nonresectable without regional lymph node involvement. Two hundred and two dogs of various breeds, were enrolled, 161 received KINAVET-CA1 at a starting dose of 12.5 mg/kg orally and 41 received placebo, daily for 6 months, or until disease progression or withdrawal from the study for another cause.

The primary variable, objective response rate after 4 months of treatment, confirmed after 6 months of treatment, failed to show a statistically significant difference between the KINAVET-CA1 and placebo treated dogs: 16.1% of dogs administered KINAVET-CA1 had a complete or partial response compared to 14.6% of dogs administered placebo.

The primary variable failed. However, one of the secondary variables, TTP, in a subpopulation of dogs that did not receive previous chemotherapy and/or radiotherapy except corticosteroids, demonstrated a reasonable expectation of effectiveness. One hundred and thirteen dogs treated with KINAVET-CA1 had an increase in median TTP of 52.5 days compared to 30 dogs treated with placebo ( $p$ -value=0.0143). The median TTP in the KINAVET-CA1 group was 118 days, 80% longer than the placebo group with a median time to progression of 65.5 days. The study was not designed for TTP to support substantial evidence of effectiveness.

## ANIMAL SAFETY:

The margin of safety and toxicity profile of masitinib (not commercial formulation) was evaluated in three laboratory safety studies (for 4, 13, and 39 weeks) in healthy 6 to 7 month old Beagle dogs. Masitinib has a narrow margin of safety, and one death occurred after 33 weeks of treatment with 20.9 mg/kg/day, a dose comparable to 1.4X the maximum KINAVET-CA1 label dose of 15.0 mg/kg/day. (See Safety Study Results, below. See Table 3, WARNINGS and PRECAUTIONS for risk management.) The results of the safety studies provide the following toxicity profile for masitinib: bone marrow suppression (anemia, neutropenia, and bone marrow hypocellularity), evidence of red blood cell sequestration (splenic hemosiderosis), proteinuria and hypoalbuminemia without kidney lesions on histopathology, liver abnormalities (mildly increased liver enzymes, histopathologic lesions), gastrointestinal signs, and increased coagulation values. The 13-week safety study provides evidence that these adverse effects are reversible.

**Safety Studies Results:** There were no signs of toxicity at 2.1 mg/kg (0.14X) for 39 weeks or 3.5 mg/kg (0.23X) for 13 weeks.

In the 4, 13, and 39-week studies at 7.0 mg/kg (0.5X) and 10.5 mg/kg (0.7X), clinical signs included transient and infrequent vomiting, soft feces, lethargy, and muscle weakness; erythema of the neck or muzzle, pallor, mild anemia, and mild proteinuria. After 39 weeks at 7.0 mg/kg (0.5X), histopathology findings included splenic hemosiderosis, brownish pigment deposits in hepatic Kupfer cells and lymph nodes, and increased lipid tissue in the bone marrow.

In the 39-week study at 20.9 mg/kg (1.4X), a female developed severe hypoalbuminemia and proteinuria, and moderate anemia, by week 25. She was euthanized in week 33 because of ascites, emaciated appearance, decreased appetite, lateral recumbency, pallor, and severe anemia, hypoalbuminemia, hypoproteinemia, and proteinuria. She had thrombocytosis, hematuria, lymphopenia, and increased activated partial thromboplastin time (APTT), fibrinogen, and blood urea nitrogen. Necropsy and histopathology findings included pericardial, subcutaneous, and tissue edema, and severe lymphoid depletion of the thymus. Other dogs on 20.9 mg/kg (1.4X) masitinib had vomiting, lethargy, pallor, erythema of the neck, hind leg stiffness, mild anemia, neutropenia, hypoalbuminemia, and proteinuria. Histopathology findings were similar to those at 7.0 mg/kg (0.5X), but more pronounced.

In the 4 and 13-week studies at 35.1 mg/kg (2.3X), clinical signs included vomiting, diarrhea, pallor, and lethargy. Clinical pathology findings included anemia, neutropenia, decreased eosinophils, and mild hypoalbuminemia, and mild increases in APTT, fibrinogen, and liver enzymes (alanine aminotransferase and alkaline phosphatase). Histopathology findings included slight hepatocellular hypertrophy, bile canicular plugs, vacuolated and brownish pigment-laden Kupfer cells in the liver, cystic epithelial hyperplasia of the gall bladder, foamy macrophages in the mesenteric lymph node, chronic interstitial pneumonitis, acute esophagitis, increased lipid tissue in the bone marrow, and bone marrow hypocellularity.

After 13 weeks of treatment, a subset of dogs from the 35.1 mg/kg (2.3X) treatment group were given a 4-week treatment-free recovery period. At the end of this period, the recovery dogs did not have the adverse clinical pathology and histopathology findings that were observed in dogs at the end of the 13 weeks of treatment.

In the 4-week study at 105.5 mg/kg (7.0X), clinical signs, clinical pathology, and histopathology results were similar but more severe than at 35.1 mg/kg (2.3X), and also included blood-tinged feces, decreased appetite, increased heart rate, weight loss, proteinuria, hematuria, hepatomegaly, vacuolated hepatocytes, a markedly increased myeloid to erythroid ratio, lymphoid depletion of the thymus, histiocytosis in the spleen, and foamy alveolar macrophages in the lungs.

## STORAGE CONDITIONS:

Keep at controlled room temperature (15-25°C; 59-77°F), in the original packaging, away from a source of heat or humidity.

## HOW SUPPLIED:

KINAVET-CA1 is supplied in white high density polyethylene (HDPE) bottles containing 30 tablets of 50mg masitinib base or 150mg masitinib base.

## REFERENCES:

1. Veterinary co-operative oncology group – common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy in dogs and cats v1.0. *Vet Comp Oncol* 2004;2(4):195-213.

Manufactured by:  
Catalent Pharma Solutions  
Somerset, NJ 08873  
USA

Manufactured for:  
AB Science  
3, Avenue George V  
75008 – PARIS (France)

Client	AB Science
Contact	Cyrille Denariez

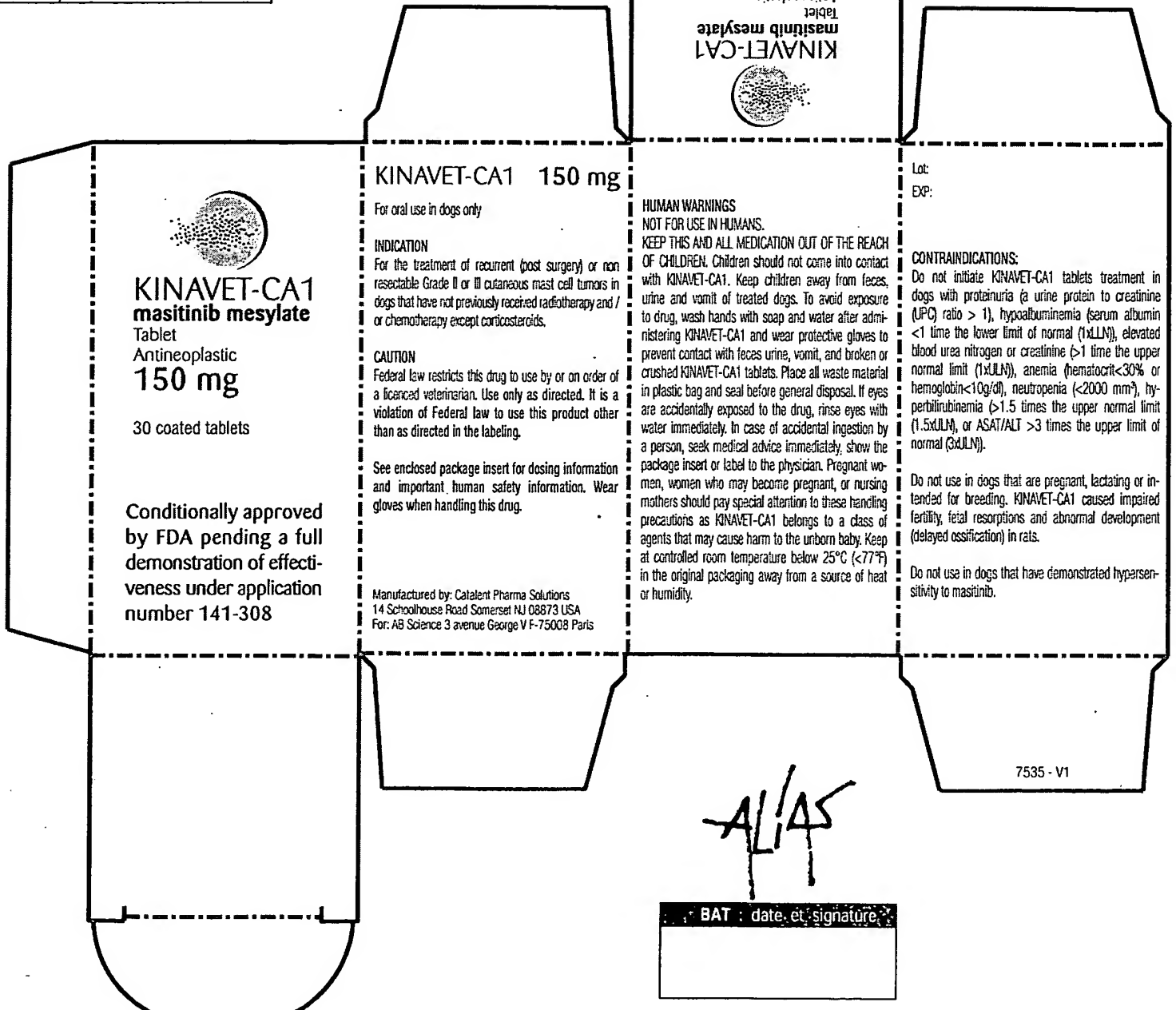
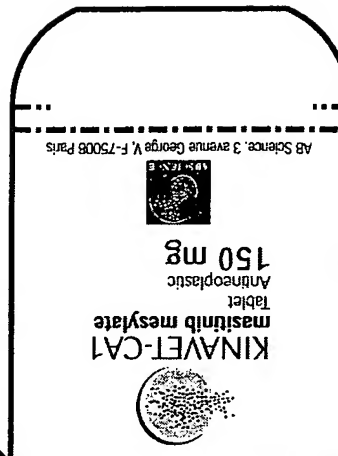
Dossier	
Produit	7531
Réf	Kinavet™ CA1
	V01
Dimensions	210x297 mm
	19/11/2010

ALIAS

BAT : date et signature

Client	AB Science
Contact	Cyrille Denariez

Dossier	7535
Produit	Kinavet™ CA1
Réf	Etui 150 mg - US - <b>V1</b>
	1 langue
Dimensions	45 x 45 x 85 mm
	19/11/2010



BAT : date, et signature

Client	AB Science
Contact	Cyrille Denariez

Dossier	7533
Produit	Knaveet™ CA
Réf	Etiquette 150 mg 1 langue - US - V1
Dimensions	110 x 45 mm
	19/11/2010

*ALIAS*

BAT : date et signature

For oral use in dogs only.

CAUTION: Federal law restricts this drug to use by or on order of a licensed veterinarian. Use only as directed. It is a violation of Federal law to use this product other than as directed in the labeling.

See enclosed package insert for dosing information and important human safety information. Wear gloves when handling this drug.

Manufactured by: Client Plasma Solutions  
14 Scotchbush Road, Springfield, NJ 08873 USA  
For AB Science 3 Avenue George V F-9508 Paris



**KINAVET-CA1**  
masitinib mesylate  
Tablet

Antineoplastic  
**150 mg**

30 coated tablets

Conditionally approved by FDA  
pending a full demonstration of  
effectiveness under application  
number 141-308

HUMAN WARNINGS:  
NOT FOR USE IN HUMANS. KEEP THIS  
AND ALL MEDICATION OUT OF THE REACH  
OF CHILDREN.  
Keep at controlled room temperature below  
25°C (77°F) in the original packaging away  
from a source of heat or humidity.

Lot:

EXP:

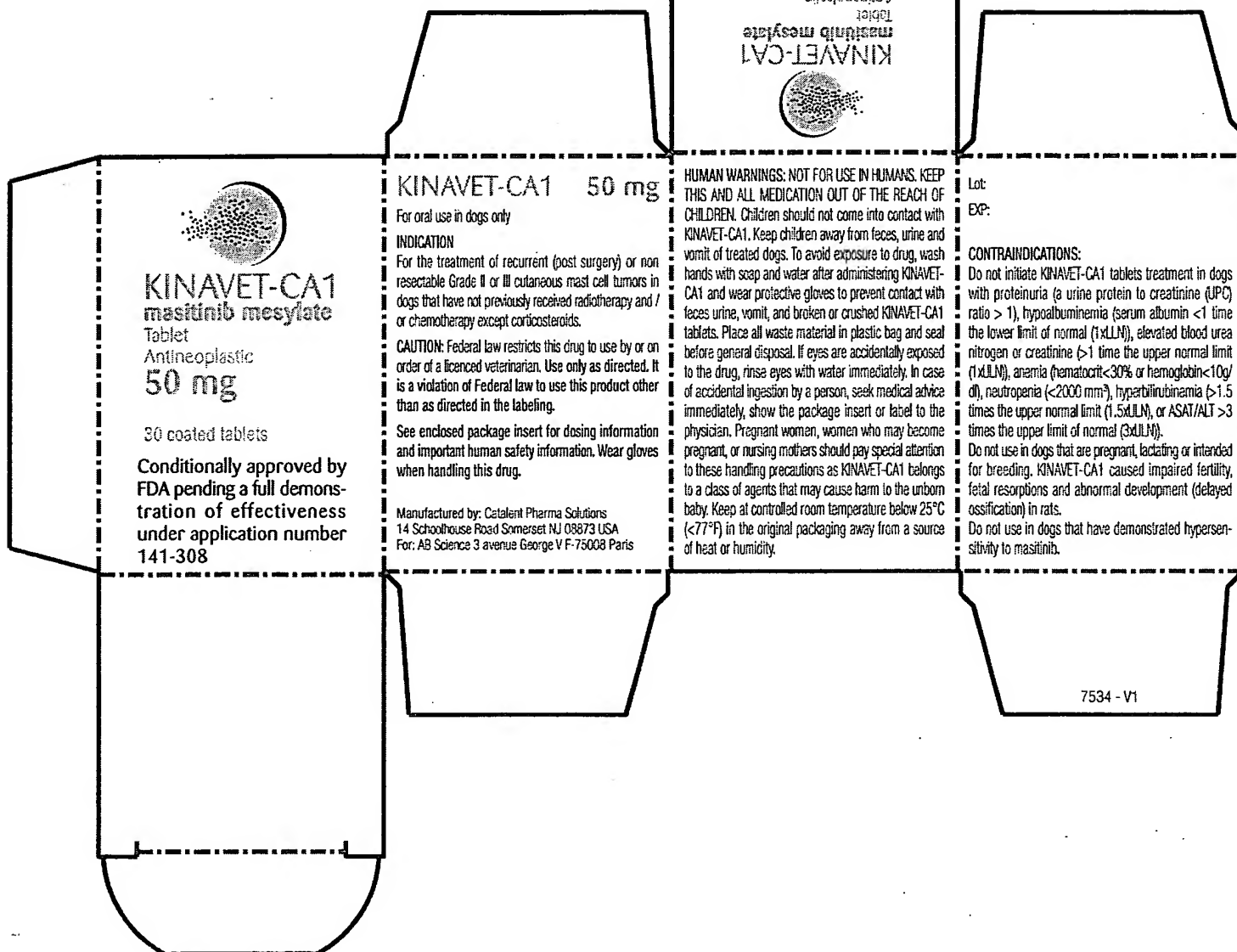
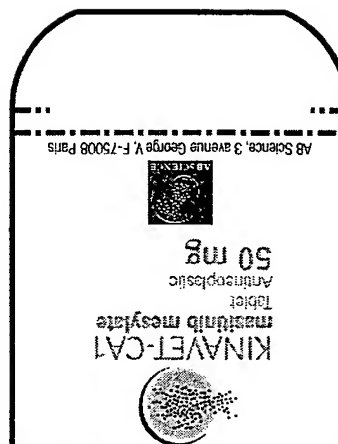
www.knaveet.com

Client	AB Science
Contact	Cyrille Denariez

Dossier	7534
Produit	Kinavet™ CA1
Réf	Etui 50 mg - US - V1
	1 langue
Dimensions	45 x 45 x 65 mm
	19/11/2010

*ALIAS*

BAT : date et signature



Client	AB Science
Contact	Cyrille Denariez

Dossier	7532
Produit	Kinavet™ CA1
Réf	Etiquette 50 mg
	1 langue US - V1
Dimensions	110 x 28 mm
	19/11/2010

ALIAS

BAT date et signature

30 coated tablets. For oral use in dogs only.  
 CAUTION: Federal law restricts this drug to use by or on order of a licensed veterinarian. Use only as directed. It is a violation of Federal law to use this product other than as directed in the labeling. See enclosed package insert for dosing information and important human safety information. Wear gloves when handling this drug.  
 Manufactured by Galaxo Pharma Solutions  
 14 Schepker Road Somerset NJ 08876 USA  
 For AS Science 3 Avenue George V F-92044 Paris



KINAVET-CA1  
 50 mg  
 30 coated tablets  
 galaxopharma

HUMAN WARNINGS: NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN. Keep at controlled room temperature below 25°C (77°F) in the original packaging away from a source of heat or humidity.  
 Lot: DP:  
 www.kinavet.com

Conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-308

## EXHIBIT D

**Application No. 141-308-A-0000-OT**  
**CONDITIONAL APPROVAL DATE: December 15, 2010**  
**CVM#201083**



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR VETERINARY MEDICINE**

**FACSIMILE TRANSMISSION**

<b>DATE:</b> December 15, 2010	<b>TIME:</b> 4:00 p.m.
<b>TO:</b> The Anson Group Attention: Michael R. Langley DVM, MBA, RAC US Agent on behalf of AB Science 11460 North Meridian Street Carmel, IN 46032	<b>FROM:</b> <input type="checkbox"/> Dr. Mary Allen <input type="checkbox"/> Dr. Mohammad Sharar <input type="checkbox"/> Ms. Bonnie Bodo <input checked="" type="checkbox"/> Dr. Robin Keyser OFFICE OF NEW ANIMAL DRUG EVALUATION HFV-107
<b>TEL.</b> 317-569-9500 Ext.103	<b>DHHS/FDA/CVM/ONADE/HFV-107</b> <b>TEL.</b> <input type="checkbox"/> (240) 276-8128 <input type="checkbox"/> (240) 276-9179 <input type="checkbox"/> (240) 276-8198 <input checked="" type="checkbox"/> (240) 276-8130
<b>FAX:</b> 317-569-9520	<b>METRO PARK NORTH II</b> 7500 STANDISH PLACE ROCKVILLE, MD 20855

Number of pages (including cover sheet): 3

CVM/ONADE FAX NUMBER: (240) 276-8242





## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Food and Drug Administration  
Rockville MD 20857

DEC 15 2010

Application Number 141308-A-0000-OT

The Anson Group  
Attention: Michael R. Langley DVM, MBA, RAC  
US Agent on behalf of AB Science  
11460 North Meridian Street  
Carmel, IN 46032

Re: Request for conditional approval of KINAVET-CA1

Dear Dr. Langley:

We conditionally approve your conditional approval application for one year for KINAVET-CA1 dated July 9, 2010, amended July 22, 2010 (M-0001), September 2, 2010 (M-0002), and September 16, 2010 (M-0003), under section 571(b) of the Federal Food, Drug, and Cosmetic Act (the act). KINAVET-CA1 (masitinib mesylate) Tablets is conditionally approved for the treatment of recurrent (post-surgery) or nonresectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and/or chemotherapy except corticosteroids in dogs. We forwarded a notice of this conditional approval for publication in the FEDERAL REGISTER. You must notify us of any change to the conditions established in this conditional approval according to 21 CFR 514.8. In addition, you must comply with the records and reporting requirements concerning post-approval experience with this conditionally approved new animal drug according to 21 CFR 514.80. If you fail to make the required reports or maintain the required records under 21 CFR 514.80, your conditional approval would be subject to the withdrawal provisions of section 571(e)(3) of the act.

This application for conditional approval is conditionally approved for one year from the date of this letter. This application is renewable annually for up to four additional one-year terms. A request to renew this application must be submitted no later than 90 days from the end of the one-year period starting on the date of this letter. This request must include sufficient information to show that you are making sufficient progress toward meeting the approval requirements under section 512(d)(1)(E) of Federal Food, Drug, and Cosmetic Act (the act), that the quantity of the drug distributed is consistent with the conditionally approved intended use and conditions of use, and the same drug in the same dosage form for the same intended use has not received approval under Section 512.

KINAVET-CA1 in the dosage form and the intended uses conditionally approved by FDA under application number 141-308 qualifies for seven years of exclusive marketing rights beginning as of the date of this conditional approval letter. Your new animal drug qualifies

Application Number 141308-A-0000-OT

Page 2

for exclusive marketing rights under section 573(c) of the Federal Food, Drug, and Cosmetic Act (the act) because it has been declared a designated new animal drug by FDA under section 573(a) of the act. Any remaining portion of the exclusive marketing period will apply to a fully approved product if there is no lapse in the conditional approval status and full approval is obtained within five years of this conditional approval.

Your final printed labeling must be identical to the approved facsimile labeling submitted September 16, 2010 (N-141308-M-0003) except change the Caution statement on the package insert, carton and bottle label, from "*Extra-label use of this drug is prohibited by Federal law.*" to "*It is a violation of Federal law to use this product other than as directed in the labeling.*" Please submit in triplicate three paper copies (a total of nine copies) of each component of the final printed labeling before distributing and marketing your new animal drug.

The expiration dating for this new animal drug is 24 months. Under current good manufacturing practice (cGMP) regulations (21 CFR 211 and 226), you are required to validate your manufacturing processes. This validation provides assurance that the manufacturing processes will reliably meet predetermined specifications. This validation is demonstrated by documenting that the manufacturing processes are adequate to preserve the identity, strength, quality, and purity of the new animal drug. If your validation information was not available or was found deficient at the time of the pre-approval inspection, you should contact FDA after you complete manufacturing validation and before you ship the product. A product that does not conform to cGMP is adulterated under section 501(a) of the act.

If you submit correspondence relating to this conditional approval, your correspondence should reference the date and the principal submission identifier found at the top of this letter. If you have any questions or comments, contact Dr. Mary E. Allen, Acting Director, Division of Therapeutic Drugs for Non-Food Animals, at 240-276-8337.

Sincerely,



Bernadette M. Dunham, D.V.M., Ph.D.

Director

Center for Veterinary Medicine

Enclosure:

Freedom of Information Summary

## EXHIBIT E

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING  
REJECTION OVER A PENDING "REFERENCE" APPLICATION**

Docket Number (Optional)

065691-0332

In re Application of: Marco Ciufolini et al.

Application No.: 10/632,101

Filed: August 1, 2003

For: 2-(3-aminoaryl)amino-4-aryl-thiazoles for the Treatment of Diseases

The owner\*, AB Science, 3 av George V, Paris, France, of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number 11/779,633, filed on July 18, 2007, as such term is defined in 35 U.S.C. 154 and 173, and as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that: any such patent; granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 39,221



Signature

April 10, 2008

Date

Rouget F. Henschel

Typed or printed name

(202) 295-4059

Telephone Number

- ☒ Terminal disclaimer fee under 37 CFR 1.20(d) is included.

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

\*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).

Form PTO/SB/96 may be used for making this statement. See MPEP § 324.

This collection of information is required by 37 CFR 1.321. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

# EXHIBIT G

Date of Approval: DEC 15 2010

# FREEDOM OF INFORMATION SUMMARY

## APPLICATION FOR CONDITIONAL APPROVAL

Application 141-308

KINAVET-CA1

Masitinib mesylate  
Tablet  
Dog

For the treatment of recurrent (post-surgery) or nonresectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and/or chemotherapy except corticosteroids

Sponsored by:

AB Science

Paris, France

## TABLE OF CONTENTS

I. GENERAL INFORMATION:.....	1
II. EFFECTIVENESS:.....	2
A. Dosage Characterization:.....	2
B. Reasonable Expectation of Effectiveness:.....	3
III. TARGET ANIMAL SAFETY:.....	5
A. Relative Bioavailability (Bridging) Study .....	5
B. 4-Week Toxicity Study .....	7
C. 13-Week Toxicity Study .....	14
D. 39-Week Toxicity Study .....	19
IV. HUMAN FOOD SAFETY: .....	25
V. USER SAFETY: .....	25
VI. AGENCY CONCLUSIONS:.....	26
A. Marketing Status: .....	26
B. Exclusivity: .....	26
C. Patent Information: .....	26
VII. ATTACHMENTS:.....	27

**I. GENERAL INFORMATION:**

**A. Application Number:** 141-308

**B. Sponsor:** AB Science  
3 Avenue George V  
75008 Paris, France

Drug Labeler Code: 052913

US Agent:  
Michael R. Langley, DVM, MBA, RAC  
The Anson Group  
11460 North Meridian Street  
Carmel, Indiana USA 46032

**C. Proprietary Name(s):** KINAVET-CA1

**D. Established Name(s):** Masitinib mesylate

**E. Pharmacological Category:** Anti-neoplastic

**F. Dosage Form(s):** Tablet

**G. Amount of Active Ingredient(s):** 50 mg or 150 mg

**H. How Supplied:** KINAVET-CA1 tablets are available as round biconvex orange coated tablets. Each tablet is engraved with the logo on one side and the mg strength on the other side. The tablets are packaged in 30-count bottles.

**I. How Dispensed:** Rx

**J. Dosage(s):** 12.5 mg/kg/day (5.7 mg/lb/day)

**K. Route(s) of Administration:** Oral

**L. Species/Class(es):** Dog

**M. Indication(s):** For the treatment of recurrent (post-surgery) or nonresectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and/or chemotherapy except corticosteroids.



## II. EFFECTIVENESS:

The active ingredient in KINAVET-CA1 is referred to as masitinib or AB1010 and the two names are used interchangeably.

**Conditional Dose:** The conditional dose for the indication “for the treatment of recurrent (post-surgery) or nonresectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and/or chemotherapy except corticosteroids” is 12.5 mg/kg/day (5.7 mg/lb/day). The safety data and reasonable expectation of effectiveness data presented in this document and the data to demonstrate a reasonable expectation of effectiveness provide support for this conditional use.

### A. Dosage Characterization:

Three toxicity studies were conducted for target animal safety and were used to help identify a conditional dose in dogs. The conditional dose of 12.5 mg/kg/day was chosen based upon the maximum tolerated dose. See TARGET ANIMAL SAFETY for more information.

In the uncontrolled field study AB03099 titled “Efficacy and Safety of AB1010 in the Treatment of Canine Mast Cell Tumors” conducted in 13 dogs with Grade II or III mast cell tumors, 10 dogs received masitinib mesylate at a dose of 12.5 mg/kg once daily, 2 dogs received 15 mg/kg twice daily and 1 dog received 4.4 mg/kg once daily. The study assessed the effectiveness and safety of masitinib mesylate on canine mast cell tumors based on objective response rate (complete and partial response) over a 12-week period. The objective tumor response was defined as the ratio of current tumor volume to baseline tumor volume and expressed as a percentage:  $\text{tumor response} = 100 \times (\text{current volume} / \text{baseline volume})$ . Complete response was defined as a tumor response equal to 0%. Partial response was defined as a tumor response  $\leq 50\%$ , with no increase in size of a previously documented lesion or development of new lesions. Four dogs were removed from analysis; 1 dog had a Grade I mast cell tumor and 3 were treated for 10 days or less. The analysis showed 2 out of 9 dogs had a complete response and 2 out of 9 had a partial response at 12 weeks. The objective response was 44% (4/9). One dog with complete response received the 4.4 mg/kg once daily dose. The other 3 dogs with objective response received the 12.5 mg/kg once daily dose. Neutropenia and vomiting were the most common adverse reactions. Edema was also seen. Two dogs were euthanized: 1 for vomiting and lethargy, and 1 for gastric ulcerations, vomiting, and increased liver values. Based on the objective response rate achieved, this study contributed to justifying 12.5 mg/kg/day as an effective dose for treatment.

Masitinib systemic bioavailability was slightly greater following co-administration with food. The effect of food on the pharmacokinetics of masitinib mesylate tablets was tested in a laboratory study of 6 male 8 month old Beagle dogs, using a crossover design and a 7-day washout period. For the fasted treatment, dogs were fasted overnight and food was given 4 hours after a dose of 11.9 mg/kg masitinib mesylate tablets. For the fed treatment, dogs were fed half of their daily ration 30 minutes before dosing and the remaining half immediately after a dose of 11.6 mg/kg masitinib mesylate tablets. The

Fed mean area under the plasma masitinib concentration time-curve (AUC) was 114% (90% Confidence Limits: 52 to 252%) of the Fasted AUC. The Fed mean peak plasma masitinib concentration ( $C_{max}$ ) was 136% (90% Confidence Limits: 98-190%) of the Fasted  $C_{max}$ , and occurred earlier. The time to peak plasma masitinib concentration ( $T_{max}$ ) occurred at 1 to 2 hours for fed versus 1 to 4 hours fasted.

**B. Reasonable Expectation of Effectiveness:**

The multi-center field study AB04003 titled "Multicentric, randomized, double-blind, placebo-controlled clinical field study to demonstrate the efficacy and safety of AB1010 in the control/treatment of Mast Cell Tumors in dogs" was evaluated to support a reasonable expectation of effectiveness for conditional approval. Two hundred and two dogs with Grade II or III mast cell tumors recurrent after surgery or nonresectable without regional lymph node or systemic involvement were enrolled. One hundred and sixty-one received KINAVET-CA1 tablets at a starting dose of 12.5 mg/kg/day and 41 received a placebo tablet. The objective was to demonstrate the effectiveness and safety of masitinib mesylate at the dose of 12.5 mg/kg/day in comparison to placebo.

Enrolled dogs had at least 1 tumor that measured a minimum of 10 mm in diameter. Dogs were excluded if they had renal insufficiency, gastrointestinal bleeding, neutropenia, elevated liver transaminases, other serious diseases, been previously treated with a tyrosine kinase inhibitor, were lactating or pregnant, intended for breeding, under 6 months of age, or weighed less than 3.3 kg.

Variables Measured

The primary evaluation of effectiveness was based on the objective response rate (complete response and partial response) after 4 months (Day 112) of treatment and confirmed after 6 months (Day 168) of treatment. See Table 1 below.

Table 1: Disease Response Definitions

Response	Definition
Complete Response (CR)	Tumor response <sup>a</sup> = 0%
Partial Response (PR)	Tumor response $\leq 51\%$ , with no increase in size of previously documented area or any new lesion development.
Stable Disease (SD)	Tumor response between 51% to 124% with no increase in size of previously documented area or any new lesion development.
Progressive Disease (PD)	All other cases.

<sup>a</sup> Tumor response =  $100 \times (\text{current volume}/\text{baseline volume})$

Secondary variables evaluated during the study included time to progression (TTP), progression-free survival, overall survival, best response rate, complete response rate at each time point, overall response rate, and control disease rate. In addition, these

variables were analyzed for different sub-populations including dogs not treated previously with chemotherapy and/or radiotherapy except corticosteroids.

The dogs were examined on day 0, 7, 14, 28, 42, 56, 84, 112, 140 and 168. Tumor assessment, complete blood count (CBC), chemistry profile and urinalysis were performed at each visit. Dose interruptions and/or dose reductions to 9 mg/kg could be made at these visits if adverse reactions occurred. Minimum hematological and biochemical values required to continue treatment at 12.5 mg/kg/day or the reduced dose: neutrophil count > 1000/ $\mu$ L, hematocrit > 20%, platelet count > 100,000/ $\mu$ L, liver transaminases  $\leq$  5.0 times the upper limit normal, and creatinine < 4.0 mg/dL.

### Results

The study, designed to measure the primary variable, objective response rate, failed to show a statistically significant difference between the masitinib mesylate and placebo treated dogs. In the intent to treat population, 16.1% of the patients on masitinib mesylate responded to treatment, compared to 14.6% on placebo. When evaluating a subpopulation of no previous chemotherapy and/or radiotherapy except corticosteroids, 18.9% of the patients on masitinib mesylate responded to treatment, compared to 10.0% on placebo. The intent to treat population included all dogs enrolled in the study.

Table 2: Objective Response Rate in the Intent to Treat Population

Objective Tumor Response	Masitinib % Response	Placebo % Response	P-value <sup>a</sup>
All dogs (n = 202)	16.1	14.6	0.831
No previous chemotherapy/ radiotherapy (n = 152)	18.9	10.0	0.294

<sup>a</sup> Exact Cochran-Mantel-Haenszel test comparing treatments, stratified on tumor grade and type

Although the primary variable failed, one of the secondary variables, time to progression, demonstrated significance in the no previous chemotherapy and/or radiotherapy except corticosteroids sub-population. The secondary variable provides the basis for reasonable expectation of effectiveness. This analysis is based on the per protocol population, which only included dogs that met the entrance criteria for the study.

Table 3: Time to Progression in the Per Protocol Population

Time to Progression	Median Masitinib (days)	Median Placebo (days)	Δ Median (days)	Δ Median (%)	P-value <sup>a</sup>
All dogs (n = 186)	112	65.5	+46.5	+71	0.1234
No previous chemotherapy/ radiotherapy (n = 143)	118	65.5	+52.5	+80	0.0143

<sup>a</sup> Log rank test comparing treatments

In the sub-population, dogs without previous chemotherapy and/or radiotherapy, the impact of masitinib mesylate on time to progression was better than in the overall population. The study was not designed for TTP to support substantial evidence of effectiveness.

#### Adverse Reactions

Adverse reactions that occurred in dogs treated with masitinib more frequently than the placebo group included vomiting, diarrhea, elevated liver enzymes, alopecia, decreased appetite, neutropenia, lethargy, cough, ocular disorders, anorexia, lymphadenopathy, subcutaneous edema, azotemia, hypoalbuminemia, hypoproteinemia, elevated urine protein creatinine ratio (UPC), proteinuria, renal failure, asthenia, lipoma, anemia, hemolytic anemia, constipation, dyspnea, circulatory collapse, dehydration, hypoglycemic seizure, pleural effusion, cardiomegaly, tachycardia, syncope, intra-abdominal hemorrhage, pancreatitis, aspiration pneumonia, back pain, spinal cord compression, inability to walk, fatigue, pruritus, behavioral changes and death.

#### Conclusion

The study results suggest there is a reasonable expectation of effectiveness for the use of KINAVET-CA1 (masitinib mesylate) tablets for the treatment of Grade II or III nonresectable or recurrent (post-surgery) cutaneous mast cell tumors in dogs not previously treated by radiotherapy and/or chemotherapy except corticosteroids.

### III. TARGET ANIMAL SAFETY:

#### A. Relative Bioavailability (Bridging) Study

- Study Title: Relative Bioavailability Study after Single Oral Administration of a Solution and Two Different Tablet Formulations to Male Beagle Dogs, Study No. 30487 PAC
- Type of Study: Laboratory study
- Study Dates: October 2005

d) Study Director and Location: Terence Appelqvist, CIT, Evreux, France

e) General Design

Purpose of Study: To compare the bioavailability of an oral solution used in the toxicity studies to the veterinary tablet.

Study Animals: Fifteen male Beagle dogs (approximately 7 months of age) were randomly allocated to three treatment groups of 5 dogs each.

Treatment Groups: Each treatment group was treated with each of the three dosage forms (solution and two different tablet forms) in a crossover design, separated by a 7-day washout period. On the three treatment days (Days 1, 8, and 15), each treatment group received a different formulation.

Drug Administration: The three dosage forms included a veterinary tablet and another tablet formulation, each containing 100 mg masitinib base, and a solution of 2.5 mg/mL masitinib base in normal saline. Over the course of the study, each dog was treated with one veterinary tablet, the other tablet, and 40 mL of solution. Tablet administration was followed with 40 mL of tap water by syringe; the solution was administered by gavage. Dogs were fasted overnight prior to each treatment, and then fed 6 hours after dosing.

Measurements and Observations: Blood samples were collected pre-dose and at 0.5, 1, 2, 3, 4, 6, 9, 12, 16, 24, and 48 hours post-dosing. The dogs were monitored for vomiting within the first hour post-dosing, mortality, clinical signs, and body weight.

Statistical Methods: Bioequivalence was assessed using 90% confidence intervals on log transformed data.

f) Results

One dog vomited after receiving the solution, and the plasma concentration data for this dog was not included in the statistical analysis. Excessive salivation was observed in this dog and in one other dog following gavage with the solution. Excessive salivation was not reported in any dogs after administration of the tablets. The results show that the bioavailability of masitinib veterinary tablets is 18% greater than the solution formulation administered by gavage. See Table 4 below.

Table 4: Pharmacokinetic Parameters Derived from Masitinib Concentrations

Parameter	Solution Mean (SD)	Veterinary Tablet Mean (SD)	90% CL <sup>a</sup>
Dose (mg/kg)	11.3 (0.5)	11.2 (0.5)	N/A
C <sub>max</sub> (ng/mL)	819 (437)	895 (283)	113 [93, 133] <sup>c</sup>
T <sub>max</sub> (hour)	1.9 (0.9)	2.3 (0.8)	N/A
AUC <sub>0-1</sub> (hr·ng/mL) <sup>b</sup>	4746 (1566)	5701 (1934)	118 [100, 137] <sup>c</sup>
Half-life (hour)	3.4 (0.3)	3.2 (0.4)	N/A
AUC <sub>0-∞</sub> (hr·ng/mL)	4790 (1586)	5758 (1969)	N/A

<sup>a</sup> CL estimated on Log Transform data. Values listed as Mean [Lower Limit, Upper Limit].

<sup>b</sup> AUC<sub>0-1</sub> values were determined by log-linear trapezoidal rule.

<sup>c</sup> Comparison: Veterinary Tablet/Solution

- g) Conclusions for the Relative Bioavailability (Bridging) Study: Masitinib veterinary tablets are 18% more bioavailable than the masitinib solution formulation administered by gavage in the toxicity studies. In the descriptions of the toxicity studies, for ease of comparison of dose group results to the label dose, this FOI Summary provides doses comparable to KINAVET-CA1 tablet doses (i.e., 18% less than the toxicity study doses of masitinib base in solution).

#### B. 4-Week Toxicity Study

- Study Title and Number: 4-Week Toxicity Study By Oral Route (Gavage) In Beagle Dogs Followed by a 2-Week Treatment-Free Period, Study No. 24371 TSC.
- Type of Study: GLP laboratory study, toxicity study with pharmacokinetics
- Study Dates: April – May 2003
- Study Director and Location: Isabelle Gaou, CIT, Evreux, France
- General Design

Purpose of Study: To evaluate the potential toxicity of an oral solution of masitinib, administered daily for 4 weeks, and the potential reversibility of findings after a subsequent 2-week treatment-free recovery period.

Study Animals: Thirty-two Beagle dogs (approximately 6 months of age) were randomly allocated to three test item groups and one control group.

Treatment Groups:

Table 5: Treatment Group Doses for the 4-Week Toxicity Study

Treatment Group	Comparable KINAVET-CA1 Tablet Dose <sup>a</sup>	Number of Dogs
Group 1 (Control)	0 mg/kg (normal saline)	5 males and 5 females
Group 2	10.5 mg/kg	3 males and 3 females
Group 3	35.1 mg/kg	3 males and 3 females
Group 4	105.5 mg/kg	5 males and 5 females

<sup>a</sup> Masitinib was administered as a solution in saline

Drug Administration: Dogs were dosed by gavage once daily at the specified dose for 4 weeks. At the end of the treatment period, two males and two females of the control and the 35.1 mg/kg and 105.5 mg/kg groups were evaluated for a 2-week treatment-free recovery period.

Measurements and Observations: The dogs were monitored for mortality, clinical signs, body weight, food consumption, ophthalmic changes, electrocardiograph recordings, hematological, blood biochemical, bone marrow evaluation, toxicokinetics, and urinalysis. On completion of the treatment or treatment-free period, designated dogs were euthanized and underwent full macroscopic examination, designated organs were weighed and selected tissue specimens were preserved for microscopic examination.

Statistical Methods: Absolute organ weights and body weight gain (at the end of the treatment period compared to the beginning) were analyzed using an analysis of variance. The terms in the model were dose group, sex, and dose group by sex (except for testes). Variables that had baseline values measured, such as clinical pathology and heart rate, were analyzed using analysis of covariance. The terms in the model were the dose group, sex, dose group by sex, and baseline. For the 8 dogs (4 in Group 1, and 4 in Group 4) that went through the treatment-free period, only the data collected during the treatment period were used in the analysis.

f) Results

Dose related trends for clinical signs are shown in Table 6.

Table 6: Incidence of Clinical Signs in the 4-Week Toxicity Study

Clinical Sign	Group 1 (n=10)	Group 2 <sup>a</sup> (n=6)	Group 3 <sup>a</sup> (n=6)	Group 4 <sup>a</sup> (n=10)
Pallor	0	0	5	10
Soft stool to diarrhea				
Incidence	0	2	4	10
Frequency in affected dogs		1-2x/dog <sup>b</sup>	1-3x/dog	2-8x/dog
Blood-tinged feces	0	0	0	4
Vomiting or regurgitation				
Incidence	0	2	6	10
Frequency in affected dogs		2-3x/dog	4-11x/dog	12-23x/dog
Excessive salivation <sup>c</sup>				
Incidence	0	2	6	10
Frequency in affected dogs		2-3x/dog	8-18x/dog	10-20x/dog
Lethargy	0	1 (< 1 day)	0	1 (3 days)
Weight loss >5%, Day 1-28	0	0	0	4
Death	0	0	0	1 <sup>d</sup>

<sup>a</sup> Groups 2, 3, and 4 were treated with daily doses of masitinib solution comparable to KINAVET-CA I tablet doses of 10.5 mg/kg, 35.1 mg/kg, and 105.5 mg/kg, respectively.

<sup>b</sup> Frequency in affected dogs denoted as 1-2x/dog means: 1 to 2 times per dog.

<sup>c</sup> Excessive salivation was related to gavage of masitinib solution.

<sup>d</sup> The dog that became recumbent and died on Day 29 had lesions compatible with aspiration (acute esophagitis and pneumonitis).



Dose related trends in selected clinical pathology test results are shown in Table 7.

Table 7: Incidence of Selected Clinical Pathology Results<sup>a</sup> in the 4-Week Toxicity Study

Variable	Group 1 (n=10)	Group 2 (n=6)	Group 3 (n=6)	Group 4 (n=10)
Anemia incidence and severity <sup>b</sup>	0	1 mild	1 moderate 3 mild	1 moderate 4 mild
Neutropenia incidence and severity <sup>c</sup>	0	1 mild	2 moderate 4 mild	1 moderate 2 mild
Hypoalbuminemia incidence and severity <sup>d</sup>	0	0	2 mild	2 moderate 7 mild
Elevated fibrinogen or APTT (activated partial thromboplastin time)	0	0	0	1 fibrinogen 1 APTT
Elevated AST & ALT <sup>e</sup>	0	0	0	1 mild
Proteinuria reported in dogs with no proteinuria at baseline <sup>f</sup>	0	0	1 low	1 moderate 5 low
Hematuria reported in dogs with no hematuria at baseline <sup>g</sup>	0	0	0	1 high 1 moderate 2 low

<sup>a</sup> Results at the end of the 4-week treatment period

<sup>b</sup> Anemia severity: mild = hemoglobin (Hb) <12-10 g/dL, moderate = Hb <10-8 g/dL

<sup>c</sup> Neutropenia severity: mild =  $2.0-3.0 \times 10^3 \mu\text{L}$ , moderate =  $1.0-1.9 \times 10^3 \mu\text{L}$

<sup>d</sup> Hypoalbuminemia severity: mild = 2.1-2.7 g/dL, moderate = 1.5-2.0 g/dL

<sup>e</sup> Elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were mild; both were less than 2 times the upper limit of the normal range.

<sup>f</sup> Proteinuria by dipstick test: low = 0.3 g/L, moderate = 1.0 g/L, high =  $\geq 3.0 \text{ g/L}$ . In these cases, proteinuria occurred in urine samples that did not have red or white blood cells on microscopic examination of the urine sediment.

<sup>g</sup> Hematuria was determined by dipstick test. Bilirubinuria was also increased in Group 4.

Statistically significant results at the end of the treatment period are shown in Table 8.

Table 8: Statistically Significant Results in the 4-Week Toxicity Study <sup>a</sup>

Variables	Treated vs. Control
Body weight gain	Group 4 < Group 1
Heart Rate	Group 4 > Group 1
<u>Hematology</u>	
Red Blood Cell Count (RBC)	Groups 2, 3 & 4 < Group 1
Hemoglobin (Hb)	Groups 2, 3 & 4 < Group 1
Packed Cell Volume (PCV)	Groups 2, 3 & 4 < Group 1
MCV <sup>b</sup>	Groups 2, 3 & 4 < Group 1
MCHC <sup>b</sup>	Groups 3 & 4 > Group 1
Neutrophil Count	Groups 2, 3 & 4 < Group 1
White Blood Cell Count (WBC)	Groups 2, 3 & 4 < Group 1
Eosinophil Count	Groups 3 & 4 < Group 1
<u>Coagulation</u>	
Fibrinogen	Group 4 > Group 1
Activated Partial Thromboplastin Time (APTT)	Group 4 > Group 1
<u>Biochemistry</u>	
Total protein	Groups 3 and 4 < Group 1
Albumin	Groups 3 and 4 < Group 1
Calcium	Groups 3 and 4 < Group 1
Creatine Kinase	Groups 3 and 4 > Group 1
Chloride	Groups 3 and 4 > Group 1
Glucose	Groups 3 and 4 > Group 1
Urea Nitrogen (BUN)	Group 4 > Group 1
Alkaline Phosphatase (ALP)	Group 4 > Group 1
Alanine Aminotransferase (ALT)	Group 4 > Group 1
<u>Absolute Organ Weight</u>	
Thymus Weight	Group 4 < Group 1

<sup>a</sup> Results at the end of the 4-week treatment period. p-values < 0.1

<sup>b</sup> Decreased MCV (mean corpuscular volume) and increased MCHC (mean corpuscular hemoglobin concentration) are consistent with a non-regenerative anemia.

Histopathologic lesions primarily involved the liver, bone marrow, and lymphatic tissue. Dose related trends in histopathology results are shown in Table 9.

Table 9: Incidence of Selected Histopathology Results<sup>a</sup> in the 4-Week Toxicity Study

Histopathology	Incidence and Severity			
	Group 1 (n=6)	Group 2 (n=6)	Group 3 (n=6)	Group 4 (n=6)
Vacuolated hepatocytes <sup>b</sup>	1 minimal	0	1 minimal	1 marked 1 moderate
Vacuolated Kupffer cells <sup>b</sup>	0	0	1 slight 3 minimal	1 marked 2 moderate 2 slight 1 minimal
Brownish pigment laden Kupffer cells	0	0	2 minimal	5 minimal
Bile canicular plugs	0	0	4 minimal	3 slight 3 minimal
Bone marrow hypo-cellularity <sup>c</sup>	0	0	1 marked 3 moderate 2 slight	2 marked 2 moderate 2 slight
Bone marrow lipoid tissue <sup>c</sup>	6 minimal	1 slight 5 minimal	4 marked 2 moderate	4 marked 2 moderate
Lymphoid depletion of the thymus	1 moderate 1 slight	4 minimal	1 slight 3 minimal	2 marked 1 slight 2 minimal
Foamy macrophages in the mesenteric lymph node (LN)	0	0	5 minimal	2 slight 3 minimal
Decreased germinal centers in the mandibular LN	0	0	0	2 slight
Lymphoid depletion of the spleen	0	0	0	1 slight
Histiocytosis of the spleen	0	0	0	2 slight 2 minimal
Foamy alveolar (lung) macrophages	0	3 minimal	2 minimal	3 slight 2 minimal
Acute esophagitis	0	0	1 slight	1 marked 1 moderate

<sup>a</sup> Results of dogs necropsied at the end of the 4-week treatment period

<sup>b</sup> Of the six Group 4 dogs necropsied at the end of the 4-week treatment period, three had grossly enlarged livers with moderate to marked vacuolization of hepatocytes and/or Kupffer cells on histopathology.

<sup>c</sup> Bone marrow histopathology is consistent with bone marrow cytology on dogs necropsied at the end of the 4-week treatment period, which showed a dose dependent increase in the myeloid to erythroid ratio.

On completion of the 2-week recovery period, a partial reversibility was noted in animals from Group 4. See Table 10.

Table 10: Clinical Findings at the End of the 2-Week Recovery Period

Findings	Incidence	
	Group 1 (n=4)	Group 4 (n=4)
Pallor	0	4
Anemia, mild	0	1
Regenerative anemia, mild (increased reticulocyte count)	0	4
Increased platelet count, mild	0	1
Hypoalbuminemia, mild	0	1
Grey/green colored livers at necropsy with bile canaliculi plugs on histopathology	0	3
Liver brownish pigment laden macrophages, minimal	0	3
Liver brownish pigment laden Kupffer cells, minimal	0	1
Vacuolated Kupffer cells, minimal	0	1
Enlarged spleen	0	4

Plasma Levels of Masitinib: On the first day of dosing, plasma masitinib exposure increased with dose, but the increases in  $C_{max}$  and AUC were less than proportional over the three doses tested. This study tested doses comparable to KINAVET-CA1 tablet doses of 10.5 mg/kg (Group 2), 35.1 mg/kg (Group 3), and 105.5 mg/kg (Group 4). Inter-animal coefficients of variation in  $C_{max}$  ranged 8 to 28% and inter-animal coefficients of variation in AUC ranged 9 to 70%.

After 28 days of dosing, the increases in  $C_{max}$  and AUC were nearly proportional across the Group 2 and 3 dose range because plasma masitinib accumulation was observed (at least 26%) in Group 3. Inter-animal coefficients of variation in  $C_{max}$  ranged 14 to 19% and inter-animal coefficients of variation in AUC ranged 14 to 32%. Significant plasma masitinib accumulation ( $\geq 46\%$  on average) was observed in Group 4 after 28 days. A gender effect was not noted.

- g) **Conclusions for the 4-Week Toxicity Study:** Transient and occasional vomiting, soft feces, and lethargy occurred at a dose comparable to 0.7X the maximum label dose of 15.0 mg/kg/day. At doses comparable to 2.3X and 7X the maximum label dose, dogs had a dose-dependent increase in the incidence and severity of gastrointestinal signs (vomiting, diarrhea, blood in the feces), bone marrow suppression (hypocellularity, non-regenerative anemia, pallor, and neutropenia), proteinuria and hypoalbuminemia without associated kidney lesions on histopathology, liver abnormalities (mildly increased liver enzymes, histopathologic lesions), lymphatic tissue toxicity (lymphoid depletion and other

histopathologic lesions), and increased coagulation values. Treatment related effects were partially reversible after a 2-week treatment-free recovery period.

### C. 13-Week Toxicity Study

- a) Study Title and Number: 13-Week Toxicity Study By Oral Route (Gavage) In Beagle Dogs Followed by a 4-Week Treatment-Free Period, Study No. 24373 TCC
- b) Type of Study: GLP laboratory study
- c) Study Dates: June – October 2003
- d) Study Director and Location: Isabelle Gaou, CIT, Evreux, France
- e) General Design

Purpose of Study: To evaluate the potential toxicity of an oral solution of masitinib, administered daily for 13 weeks, and the potential reversibility of findings after a subsequent 4-week treatment-free recovery period.

Study Animals: Thirty-two Beagle dogs (approximately 6 months of age) were randomly allocated to three test item groups and one control group. One Group 4 dog died on Day 8 and was replaced by another dog.

#### Treatment Groups:

Table 11: Treatment Group Doses for the 13-Week Toxicity Study

Treatment Group	Comparable KINAVET-CA1 Tablet Dose <sup>a</sup>	Number of Dogs
Group 1 (Control)	0 mg/kg(normal saline)	5 males and 5 females
Group 2	3.5 mg/kg	3 males and 3 females
Group 3	10.5 mg/kg	3 males and 3 females
Group 4	35.1 mg/kg	5 males and 5 females

<sup>a</sup> Masitinib was administered as a solution in saline

Drug Administration: Dogs were dosed by gavage once daily at the specified dose for 13 weeks. At the end of the treatment period, two males and two females of the control and high-dose groups were evaluated for a 4-week treatment-free recovery period.

**Measurements and Observations:** The dogs were monitored for mortality, clinical signs, body weight, food consumption, ophthalmology examinations, electrocardiograph recordings, hematological, blood biochemical investigations, toxicokinetics, and urinalysis. On completion of the treatment or treatment-free period, designated dogs were euthanized and underwent full macroscopic examination, designated organs were weighed and selected tissue specimens were preserved for microscopic examination.

**Statistical Methods:** Absolute organ weights and body weight gain (at the end of the treatment period compared to the beginning) were analyzed using an analysis of variance. The terms in the model were dose group, sex, and dose group by sex (except for testes). Variables that had baseline values measured, such as clinical pathology and heart rate, were analyzed using analysis of covariance. The terms in the model were the dose group, sex, dose group by sex, and baseline. For the 8 dogs (4 in Group 1, and 4 in Group 4) that went through the treatment-free period, only the data collected during the treatment period were used in the analysis.

#### f) Results

Dose related trends in clinical signs are shown in Table 12.

Table 12: Incidence of Clinical Signs in the 13-Week Toxicity Study

Clinical Sign	Group 1 (n=10)	Group 2 <sup>a</sup> (n=6)	Group 3 <sup>a</sup> (n=6)	Group 4 <sup>a</sup> (n=11)
Pallor	0	0	0	9
Soft stool to diarrhea				
Incidence	5	4	1	7
Frequency in affected dogs	1-5x/dog	1-3x/dog	3x/dog	2-7x/dog
Vomiting or regurgitation				
Incidence	0	0	3	9
Frequency in affected dogs			1-3x/dog	1-4x/dog
Excessive salivation <sup>b</sup>				
Incidence	0	1	4	10
Frequency in affected dogs		1x/dog	1-6x/dog	≥ 20x/dog
Lethargy or weakness	0	0	1	2
Erythema of muzzle	0	0	1	0
Death	0	0	0	1 <sup>c</sup>

<sup>a</sup> Groups 2, 3, and 4 were treated with daily doses of masitinib solution comparable to KINAVET-CA1 tablet doses of 3.5 mg/kg, 10.5 mg/kg, and 35.1 mg/kg, respectively.

<sup>b</sup> Excessive salivation was related to gavage of masitinib solution.

<sup>c</sup> The Group 4 dog died shortly after dosing on Day 8 had lesions compatible with aspiration (reddish colored lungs and foamy contents in the trachea and lungs). She was replaced with another female that underwent all procedures 8 days after the rest of the dogs in her group.

Dose related trends in selected clinical pathology test results are shown in Table 13.

Table 13: Incidence of Selected Clinical Pathology Results <sup>a</sup> in the 13-Week Toxicity Study

Variable	Incidence and Severity			
	Group 1 (n=10)	Group 2 (n=6)	Group 3 (n=6)	Group 4 (n=6)
Anemia <sup>b</sup>	0	0	1 mild	1 moderate 6 mild
Neutropenia <sup>c</sup>	0	0	0	1 moderate 6 mild
Hypoalbuminemia <sup>d</sup>	0	0	0	2 mild
Elevated fibrinogen or APTT (activated partial thromboplastin time)	0	0	0	1 fibrinogen 1 APTT
Elevated alkaline phosphatase (ALP) <sup>e</sup>	0	0	0	1 mild
Elevated blood glucose <sup>f</sup>	0	0	0	1 moderate

<sup>a</sup> Results during or at the end of the 13-week treatment period

<sup>b</sup> Anemia severity: mild = Hb <12-10 g/dL, moderate = Hb <10-8 g/dL

<sup>c</sup> Neutropenia severity: mild =  $2.0-3.0 \times 10^3 \mu\text{L}$ , moderate =  $1.0-1.9 \times 10^3 \mu\text{L}$

<sup>d</sup> Hypoalbuminemia severity: mild = 2.1-2.7 g/dL, moderate = 1.5-2.0 g/dL

<sup>e</sup> ALP elevation was mild, less than 2 times the upper limit of the normal range

<sup>f</sup> Glucose was moderately elevated, at 190 mg/dL

Statistically significant results at the end of the treatment period are shown in Table 14.

Table 14: Statistically Significant Results in the 13-Week Toxicity Study <sup>a</sup>

Variables	Treated vs. Control
<u>Hematology</u>	
Red Blood Cell Count (RBC)	Groups 3 & 4 < Group 1
Hemoglobin (Hb)	Groups 3 & 4 < Group 1
Packed Cell Volume (PCV)	Groups 3 & 4 < Group 1
MCV <sup>b</sup>	Groups 3 & 4 > Group 1
MCHC <sup>b</sup>	Groups 3 & 4 < Group 1
Neutrophil Count	Group 4 < Group 1
White Blood Cell Count (WBC)	Group 4 < Group 1
Eosinophil Count	Group 4 < Group 1
Platelet Count	Group 4 > Group 1
<u>Coagulation</u>	
Fibrinogen	Group 4 > Group 1
Activated Partial Thromboplastin Time (APTT)	Groups 3 & 4 > Group 1
<u>Biochemistry</u>	
Albumin	Group 4 < Group 1
Calcium	Group 4 < Group 1
Potassium	Group 4 > Group 1
Chloride	Group 4 > Group 1
Alkaline Phosphatase (ALP)	Group 4 > Group 1
Alanine Aminotransferase (ALT)	Group 4 > Group 1
<u>Absolute Organ Weight</u>	
Liver Weight	Groups 3 & 4 > Group 1

<sup>a</sup> Results at the end of the 13-week treatment period, p-values < 0.1

<sup>b</sup> Increased MCV (mean corpuscular volume) and decreased MCHC (mean corpuscular hemoglobin concentration) are opposite from the 4-week toxicity study results (Study No. 24371 TSC).



Histopathologic lesions primarily involved the liver, gall bladder, bone marrow, and lungs. Dose related trends in histopathology results are shown in Table 15.

Table 15: Incidence of Selected Histopathology Results<sup>a</sup> in the 13-Week Toxicity Study

Lesions	Incidence and Severity			
	Group 1 (n=6)	Group 2 (n=6)	Group 3 (n=6)	Group 4 (n=6)
Hepatocellular hypertrophy	0	0	0	2 slight 4 minimal
Brownish pigment laden Kupffer cells	0	0	0	1 slight
Gall bladder cystic epithelial hyperplasia	0	0	0	2 slight
Bone marrow lipid tissue	1 moderate 2 slight 1 minimal	1 slight 3 minimal	1 moderate 1 slight 3 minimal	3 marked 2 minimal
Chronic interstitial pneumonitis	1 minimal	0	0	2 moderate

<sup>a</sup> Results of dogs necropsied at the end of the 13-week treatment period

On completion of the 4-week recovery period, the adverse findings previously recorded for dogs in Group 4 were no longer observed.

Plasma Levels of Masitinib: On the first day of dosing plasma masitinib exposure increased with dose and appeared to be dose proportional over the three doses tested. This study tested doses comparable to KINAVET-CA1 tablet doses of 3.5 mg/kg (Group 2), 10.5 mg/kg (Group 3), and 35.1 mg/kg (Group 4). Inter-animal coefficients of variation in  $C_{max}$  ranged 35 to 56% and inter-animal coefficients of variation in AUC ranged 38 to 59%.

After 13 weeks of daily dosing increases in  $C_{max}$  and AUC were more than dose proportional for Group 3 and Group 4 compared to Group 2. However,  $C_{max}$  and AUC values were proportional in Groups 3 and 4. Inter-animal coefficients of variation in  $C_{max}$  ranged 19 to 95% and inter-animal coefficients of variation in AUC ranged 23 to 101%. Plasma masitinib exposure accumulation was variable (20 to > 200 %) in Groups 3 and 4 after 13 weeks of daily dosing. A gender effect was not noted.

- g) Conclusions for the 13-Week Toxicity Study: Transient and occasional vomiting, muscle weakness, erythema of the muzzle, and mild anemia occurred at a dose comparable to 0.7X the maximum label dose of 15.0 mg/kg/day. At a dose comparable to 2.3X the maximum label dose, dogs had vomiting, diarrhea, lethargy, and mild hypoalbuminemia. The dogs also had evidence of bone marrow suppression (increased lipid tissue in the bone marrow, anemia, pallor,

and neutropenia), liver abnormalities (mildly increased liver enzymes, histopathologic lesions), and increased coagulation values. Treatment related effects were no longer observed (reversed) after a 4-week treatment-free recovery period.

#### D. 39-Week Toxicity Study

- a) Study Title and Number: 39-Week Toxicity Study By Oral Route (Gavage) In Beagle Dogs, Study No. 26100 TCC.
- b) Type of Study: GLP laboratory study
- c) Study Dates: August 2003 – May 2004.
- d) Study Director and Location: Isabelle Gaou, CIT, Evreux, France
- e) General Design

Purpose of Study: To evaluate the potential toxicity and pharmacokinetics of an oral solution of masitinib, administered daily for 39 weeks.

Study Animals: Thirty-two Beagle dogs (approximately 7 months of age) were randomly allocated to three test item groups and one control group of 4 males and 4 females each.

#### Treatment Groups:

Table 16: Treatment Group Doses for the 39-Week Toxicity Study

Treatment Group	Comparable KINAVET-CA1 Tablet Dose <sup>a</sup>	Number of Dogs
Group 1 (Control)	0 mg/kg (normal saline)	4 males and 4 females
Group 2	2.1 mg/kg	4 males and 4 females
Group 3	7.0 mg/kg	4 males and 4 females
Group 4	20.9 mg/kg	4 males and 4 females

<sup>a</sup> Masitinib was administered as a solution in saline

Drug Administration: Dogs were dosed by gavage daily at the specified level for 39 weeks.

Measurements and Observations: The dogs were monitored for mortality, clinical signs, body weight, food consumption, ophthalmology examinations, electrocardiograph recordings, hematological, blood biochemical investigations, toxicokinetics, and urinalysis. On completion of the treatment period, the dogs

were euthanized and underwent full macroscopic examination, designated organs were weighed and selected tissue specimens were preserved for microscopic examination.

Statistical Methods: Absolute organ weights and body weight gain (at the end of the study compared to the beginning) were analyzed using an analysis of variance. The terms in the model were dose group, sex, and dose group by sex (except for testes). Variables which were measured multiple times during the study (including baseline measurements), such as clinical pathology and heart rate, were analyzed using a repeated measures analysis of covariance. The terms in the model were dose group, study day, sex, all their two- and three-way interactions, and baseline.

f) Results

Mortality: One Group 4 female was euthanized prematurely on Day 225 (Week 33). During the weeks preceding euthanasia, she developed a swollen abdomen due to ascites, emaciated appearance, pallor, decreased appetite, lethargy, loss of balance, tremors, lateral recumbency, severe anemia, marked thrombocytosis, lymphopenia, increased APTT and fibrinogen, severe hypoalbuminemia and hypoproteinemia, increased blood urea nitrogen and creatine kinase, severe proteinuria, hematuria without red cells, and decreased urine pH. Histopathology findings included edema in the pericardium, thymus, subcutaneous tissue, pancreas and adjacent lymph nodes, and severe lymphoid depletion in the thymus.

Dose related trends in clinical signs are shown in Table 17.

Table 17: Incidence of Clinical Signs in the 39-Week Toxicity Study

Clinical Sign	Group 1 (n=8)	Group 2 <sup>a</sup> (n=8)	Group 3 <sup>a</sup> (n=8)	Group 4 <sup>a</sup> (n=8)
Pallor	0	0	1	8
Soft stool to diarrhea				
Incidence	4	0	4	6
Frequency in affected dogs	1-5x/dog		1-2x/dog	1-3x/dog
Vomiting or regurgitation				
Incidence	1	1	2	6
Frequency in affected dogs	1x	1x	1-4x/dog	1-3x/dog
Excessive salivation <sup>b</sup>				
Incidence	1	3	8	8
Frequency in affected dogs	1x	1-3x/dog	1-12x/dog	≥ 68x/dog
Lethargy	0	0	2	3
Lateral recumbency	0	0	0	2
Hind leg stiffness	0	0	0	1
Erythema of the neck	0	0	1	2
Depigmentation of eyelids	0	0	0	1
Reported to be emaciated in the last 3 weeks of the study	1	2	0	4
Death	0	0	0	1 <sup>c</sup>

<sup>a</sup> Groups 2, 3, and 4 were treated with daily doses of masitinib solution comparable to KINAVET-CA1 tablet doses of 2.1 mg/kg, 7.0 mg/kg, and 20.9 mg/kg, respectively.

<sup>b</sup> Excessive salivation was related to gavage of masitinib solution.

<sup>c</sup> The dog that was euthanized in Week 33 is described above.

Dose related trends in selected clinical pathology test results are shown in Table 18.

Table 18: Incidence of Selected Clinical Pathology Results<sup>a</sup> in the 39-Week Toxicity Study

Variable	Group 1 (n=8)	Group 2 (n=8)	Group 3 (n=8)	Group 4 (n=8)
Anemia <sup>b</sup> : Incidence and Severity	0	0	2 mild	1 very severe 6 mild
Neutropenia <sup>c</sup> : Incidence and Severity	0	0	0	4 mild
Hypoalbuminemia <sup>d</sup> : Incidence and Severity	0	0	0	1 severe 2 mild
Elevated Fibrinogen or APTT (Activated partial thromboplastin time)	0	0	0	2 Fibrinogen 1 APTT
Proteinuria reported in dogs with no proteinuria at baseline <sup>e</sup>	0	1 low	3 low	2 high 3 low

<sup>a</sup> The worst result reported for each dog during the 39-week study

<sup>b</sup> Anemia: mild = Hb <12-10 g/dL. The dog with very severe anemia had a Hb of 3.9 g/dL prior to euthanasia in Week 33.

<sup>c</sup> Neutropenia: mild = 2.0-3.0 x 10<sup>3</sup> µL, moderate = 1.0-1.9 x 10<sup>3</sup> µL

<sup>d</sup> Hypoalbuminemia: mild = 2.1-2.7 g/dL, moderate = 1.5-2.0 g/dL, severe < 1.5 g/dL

<sup>e</sup> Proteinuria by dipstick test: low = 0.3 g/L, moderate = 1.0 g/L, high = ≥ 3.0 g/L. In these cases, proteinuria occurred in urine samples that did not have red or white blood cells on microscopic examination of the urine sediment.

Statistically significant results are shown in Table 19.

Table 19: Statistically Significant Results in the 39-Week Toxicity Study <sup>a</sup>

Variables	Treated vs. Control
<u>Dose group*day significant for hematology and coagulation</u>	
RBC	Groups 3 & 4 < Group 1 at Weeks 13, 25, and 38
Hemoglobin	Groups 3 & 4 < Group 1 at Weeks 13, 25, and 38
PCV	Groups 3 & 4 < Group 1 at Weeks 13, 25, and 38
MCV <sup>b</sup>	Group 3 > Group 1 at Week 13 Group 4 > Group 1 at Weeks 13, 25, and 38
Neutrophil Count	Group 3 < Group 1 at Weeks 25 and 38 Group 4 < Group 1 at Weeks 13, 25, and 38
Eosinophil Count	Group 4 < Group 1 at Week 38
<u>Dose group main effect significant for hematology and coagulation</u>	
MCHC <sup>b</sup>	Groups 3 & 4 < Group 1
WBC	Group 4 < Group 1
Platelets	Group 4 > Group 1
APTT	Group 4 > Group 1
Prothrombin time	Group 4 > Group 1
<u>Dose group main effect significant for biochemistry</u>	
Total protein	Groups 3 & 4 < Group 1
Albumin	Group 4 < Group 1
Calcium	Group 4 < Group 1
<u>Dose group*day significant for biochemistry</u>	
Sodium	Groups 3 & 4 < Group 1 at Week 38
Glucose	Group 4 > Group 1 at Weeks 13 and 25
<u>Dose group main effect significant for absolute organ weight</u>	
Heart Weight <sup>c</sup>	Groups 2, 3 & 4 > Group 1

<sup>a</sup> p-values < 0.1

<sup>b</sup> Increased MCV (mean corpuscular volume) and decreased MCHC (mean corpuscular hemoglobin concentration) are consistent with the 13-week study results, but the opposite of the 4-week study results.

<sup>c</sup> Mean absolute organ weights excluding the Group 4 female euthanized at Week 33

Histopathologic lesions primarily involved the spleen, liver, bone marrow, and lymphatic tissue. Dose related trends in histopathology results are shown in Table 20.

Table 20: Incidence of Selected Histopathology Results in the 39-Week Toxicity Study

Lesions	Incidence and Severity			
	Group 1 (n=8)	Group 2 (n=8)	Group 3 (n=8)	Group 4 (n=8)
Generalized edema	0	0	0	1 <sup>a</sup>
Increased iron deposits in the spleen (hemosiderosis)	1 slight 6 minimal	5 slight 3 minimal	5 moderate 2 slight 1 minimal	4 marked 4 moderate
Brownish pigment laden Kupffer cells <sup>b</sup>	0	0	2 minimal	1 moderate 3 slight 3 minimal
Liver positive for iron	0	1 minimal	2 minimal	3 minimal
Mandibular lymph node positive for iron	0	2 minimal	4 minimal	5 minimal
Bone marrow lipoid tissue	3 slight 5 minimal	3 moderate 3 slight 2 minimal	2 marked 3 moderate 2 slight 1 minimal	4 marked 4 moderate
Lymphoid depletion of the thymus <sup>c</sup>	1 moderate 5 slight 2 minimal	3 moderate 3 minimal	4 moderate 2 minimal	1 massive 1 marked 2 moderate 2 slight 2 minimal
Vacuolated seminiferous tubules and oligospermia	0/4 males	0/4 males	0/4 males	2/4 males (slight to moderate)

<sup>a</sup> The dog that was euthanized at Week 33 had ascites, subcutaneous edema, and edema of the thymus, pancreas and associated lymph nodes.

<sup>b</sup> One Group 4 male had an enlarged grey/green colored liver on gross necropsy.

<sup>c</sup> On gross necropsy, small thymus glands were reported in 2/8 Group 1, 1/8 Group 2, 2/8 Group 3, and 4/8 Group 4 dogs.

**Plasma Levels of Masitinib:** On the first day of dosing, the plasma masitinib exposure increased with dose; based on the Group 2 dose the increase in  $C_{max}$  and AUC values was more than dose proportional after the first dose. However, the increases in  $C_{max}$  and AUC appear to be proportional across the Group 3 and 4 dose range. This study tested doses comparable to KINAVET-CA1 tablet doses of 2.1 mg/kg (Group 2), 7.0 mg/kg (Group 3), and 20.9 mg/kg (Group 4). Inter-animal coefficients of variation in  $C_{max}$  ranged 20 to 39% and inter-animal coefficients of variation in AUC ranged 25 to 41%.

After 39 weeks of exposure the  $C_{max}$  and AUC values at higher doses appear to decrease compared to the Group 2 dose because exposure accumulation was

observed in Group 2. Exposure accumulation was not observed in Groups 3 or 4. This observation is in agreement with the results for Group 2 in the 4-week toxicity study, which was treated with a dose comparable to a KINAVET-CA1 tablet dose of 10.5 mg/kg. Inter-animal coefficients of variation in  $C_{max}$  ranged 24 to 59% and inter-animal coefficients of variation in AUC ranged 23 to 38%. A gender effect was not noted.

- g) Conclusions for the 39-Week Toxicity Study: Vomiting, lethargy, erythema of the neck, mild anemia, proteinuria, hemosiderosis of the spleen, and increased lipid tissue in the bone marrow occurred at a dose comparable to 0.5X the maximum label dose of 15.0 mg/kg/day. At a dose comparable to 1.4X the maximum label dose, a dog was euthanized because of severe anemia, hypoproteinemia, proteinuria, pericardial effusion, ascites, emaciated appearance, and lateral recumbency. In that dose group, masitinib toxicity was characterized by gastrointestinal signs (vomiting, diarrhea), general signs (lethargy, hind leg stiffness, erythema of the neck), bone marrow suppression (increased lipid tissue in the bone marrow, anemia, pallor, and neutropenia), evidence of red blood cell sequestration (hemosiderosis of the spleen), proteinuria and hypoalbuminemia without associated kidney lesions on histopathology, liver abnormalities (histopathologic lesions), lymphatic tissue toxicity (lymphoid depletion), and increased coagulation values.

#### IV. HUMAN FOOD SAFETY:

This drug is intended for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

#### V. USER SAFETY:

The product labeling contains the following information regarding safety for humans handling, administering, or exposed to KINAVET-CA1:

**NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.** Children should not come into contact with KINAVET-CA1. Keep children away from feces, urine, or vomit of treated dogs.

To avoid exposure to drug, wash hands with soap and water after administering KINAVET-CA1 and wear protective gloves to prevent contact with feces, urine, vomit, and broken or crushed KINAVET-CA1 tablets. Place all waste material in a plastic bag and seal before general disposal. If eyes are accidentally exposed to the drug, rinse eyes with water immediately. In case of accidental ingestion by a person, seek medical advice immediately, show the package insert or label to the physician.



Pregnant women, women who may become pregnant, or nursing mothers should pay special attention to these handling precautions (see handling instructions above). KINAVET-CA1 may harm an unborn baby (cause birth defects). For pregnant and nursing women, accidental ingestion of KINAVET-CA1 may have adverse effects on pregnancy or the nursing baby.

## **VI. AGENCY CONCLUSIONS:**

The data submitted in support of this application satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act. The data demonstrate that KINAVET-CA1, when used according to the label, is safe and has a reasonable expectation of effectiveness for the treatment of recurrent (post-surgery) or nonresectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and/or chemotherapy except corticosteroids.

### **A. Marketing Status:**

KINAVET-CA1 is conditionally approved for one year from the date of approval and is annually renewable for up to four additional one-year terms.

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to properly diagnose mast cell tumors and to monitor safe use of the product, including treatment of any adverse reactions.

### **B. Exclusivity:**

KINAVET-CA1 in the dosage form and for the intended uses conditionally approved by FDA under application number 141-308 qualifies for seven years of exclusive marketing rights beginning as of the date of conditional approval. This new animal drug qualifies for exclusive marketing rights under section 573(c) of the Federal Food, Drug, and Cosmetic Act (the act) because it has been declared a designated new animal drug by FDA under section 573(a) of the act.

### **C. Patent Information:**

KINAVET-CA1 is under the following U.S. patent numbers:

<u>U.S. Patent Number</u>	<u>Date of Expiration</u>
7,423,055	August 1, 2023

For current information on patents, see the Animal Drugs @ FDA database (formerly the Green Book) on the FDA CVM internet website.

**VII. ATTACHMENTS:**

Labeling:  
Package Insert  
Client Information Sheet

## EXHIBIT H



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

INAD 011206 A-0000

AB Science  
Attention: Anne-Virginie Eggimann, M.Sc.  
Consultant  
38 rue Vauthier  
92100 Boulogne  
France

MAR 11 2004

Dear Ms. Eggimann:

We refer to your submission dated November 24, 2003, (A-0000), wherein you requested an Investigational New Animal Drug (INAD) exemption for the use of AB1010. The drug product is proposed for the treatment of mast cell tumors in dogs. Your submission also requested a presubmission conference to discuss the development of your product in the United States. Under cover letter dated January 5, 2004, (T-0001) you submitted a request for a categorical exclusion from preparing an environmental assessment.

For administrative purposes, we have assigned you INAD number 011206 for the use of AB1010 in canines. Please refer to this number in all drug shipments and correspondence concerning the drug while it is in the investigational stage. Future correspondence regarding this submission to your INAD file should be identified by the submission's correspondence date and our file number, INAD 011206 A-0000 and submitted directly to the Document Control Unit (HFV-199).

Please find enclosed CVM's minutes from the presubmission conference, which took place on December 18, 2003.

Your claim for the investigational use of AB1010 falls within the categorical exclusion in 21 CFR 25.33(e). Your submission states that to your knowledge, no extraordinary circumstances exist which may significantly affect the human environment. Therefore, neither an environmental assessment (EA) nor an environmental impact statement is required. This categorical exclusion from preparation of an EA and an Environmental Impact Statement does not relieve you of the responsibility for determining and meeting all Federal, State, and local environmental and occupational laws and regulations that apply to the manufacturing, use, and disposal of the investigational drugs.

Prior to shipment of the new animal drug for clinical tests in animals, you must submit in triplicate a "Notice of Claimed Investigational Exemption for a New Animal Drug", in accordance with 21 CFR 511.1(b)(4).

Investigational labeling should be affixed to your investigational drug product prior to shipment for studies conducted under 21 CFR 511.1(a) or (b), as appropriate.

If you have any questions or if you need further assistance, please contact, Elizabeth A. Luddy, Leader, Companion and Wildlife Team. The telephone number is (301) 827-7540.

Sincerely yours,



Melanie R. Berson, DVM  
Director  
Division of Therapeutic Drugs  
for Non-Food Animals  
Office of New Animal Drug Evaluation  
Center for Veterinary Medicine

Enclosure

I-011206-A-0000  
AB1010  
Canine  
AB Science  
38 rue Vauthier  
92100 Boulogne  
France  
December 18, 2003

**Memorandum of Presubmission Conference  
December 18, 2003, 1 – 3 pm**

**Attendees:**

**CVM:** Melanie Berson, HFV-110  
Elizabeth Luddy, HFV-112  
Lisa Troutman, HFV-112  
Douglass Oeller, HFV-112  
Anna Nevius, HFV-105  
Marilyn Martinez, HFV-130  
June Liang, HFV-143  
Glen Ghiorghis, HFV-143

**AB Science**

Alain Moussy  
Olivier Hermine  
Des Curran  
Philippe Reginault  
Laurent Guy  
Marie-Paul Lachaud Lefay – ICON  
Leland Vickers – ICON  
Anne-Virgine Eggimann – Consultant  
Emmanuelle Voisin – Consultant

**Background:**

The sponsor provided background information regarding the incidence of Mast Cell Tumors (MCT) in dogs. The histological grading system and survival data associated with the different grades was discussed.

**Drug Characteristics:**

The drug is referred to by two different names. AB1003 is the free base form of the drug. It is the drug referenced for the dosage (i.e., 12.5 mg/kg refers to AB1003). AB1010 is the salt form of the drug and is the final market formulation.

The drug is selective to c-kit and PDGF-beta. It does not interact with other tyrosine kinases thereby possibly reducing toxicity. The sponsor has not encountered any

evidence that there is any multi-drug resistance developed after long-term administration of the drug. There is evidence to suggest that it protects against developing resistance in human CML if there is continual pressure on the cells.

The presence of c-kit varies between patients. However, if c-kit is present, it will be in all cells within a MCT because c-kit is the cause of the mutation creating the tumor.

**Effectiveness:**

The sponsor is planning to conduct a multi-location, uncontrolled field study. The study will enroll 110 dogs with either Grade II or Grade III MCTs with or without previous treatments. Dogs may be enrolled with metastases at the discretion of the investigator. It will be conducted at 24 locations including 12 in the United States, five in the United Kingdom, two in the Netherlands, two in Germany, two in France and one in Slovenia. Two thirds of the cases will come from the United States and the remaining one third from the European countries. Locations in the United States will be with board certified oncologists.

CVM questioned whether a central laboratory will perform the histopathology and the clinical chemistry. The sponsor stated that many of the dogs will have had histopathology conducted prior to consideration for inclusion into the study. If possible, the sponsor will obtain histopathology slides to confirm the diagnosis and grading. It would be very difficult to provide a central pathologist for the study. CVM recommended that the sponsor should address the comparability of the scoring from different pathologists in the protocol. Clinical chemistry analysis will be conducted at a central laboratory in the United States.

CVM strongly suggested the sponsor submit the protocol for review to obtain protocol concurrence prior to starting the study. A dosage rationale should be included with the protocol along with scientific justification and rationale for using complete response (CR) + partial response (PR) > 20% for the success criteria. Scientific justification for conducting an uncontrolled study should also be included. Scientific literature from peer reviewed journals or similar sources, documenting the course of disease if untreated should be utilized to justify a historical control.

CVM suggested that if the sponsor was interested, they should submit a second protocol for extended use. It would allow dogs enrolled in the field study to continue receiving drug after the pivotal field study has been completed.

The sponsor presented their proof of concept. A 6 year old Chow Chow in South Africa had two Grade III MCTs with lymph node involvement. The dog was administered 5 mg/kg BID for 63 days. At the end of 63 days, there was no evidence of MCT's or lymph node involvement.

The sponsor asked if they could stop the study if 17 successes were seen after enrolling 55 patients. CVM stated it would be unlikely that we could concur with the proposal. CVM's regulations do not provide for orphan drug status or conditional approvals. Nor

do we have the legal authority to require additional studies after the initial approval. We need to gather both safety and effectiveness data from the field study. There should be enough dogs treated to provide inferential value.

Interim analysis was also discussed. CVM stated that it is not standard practice for us to allow interim analysis. However, the proposal may be included in the protocol for review.

**Target Animal Safety Studies (Nonclinical Studies):**

The sponsor has conducted multiple nonclinical studies in rats and dogs. A 28-day oral toxicity study was conducted in dogs by administering 0, 15, 50, and 150 mg/kg/day by gavage. It was concluded that the No Observable Adverse Effect Level (NOAEL) is 15 mg/kg. At 15 mg/kg/day, transient vomiting and diarrhea were noted. The NOEL determination will be used to justify the starting dose in the field study.

Results from the 13-week oral toxicity study in dogs are pending. Dogs were dosed at 0, 4, 12, and 41 mg/kg/day by gavage.

The sponsor is currently conducting a 9-month oral toxicity study in dogs. Dogs were dosed at 0, 5, 15, and 50 mg/kg/day by gavage. CVM stated that this study is needed to obtain an open ended label to allow continual use of the drug. Typically a 6 month target animal safety study is necessary at 1, 3, and 5 times the recommended dosage. CVM stated the 1X dose is considered to be 20 mg/kg/day, the maximum dose administered in the field study. The purpose of administering multiples dosages of the drug is to define the toxic syndrome and therapeutic index. The studies conducted to date and this study may be acceptable to support the target animal safety technical section based upon the toxicities observed at dosages above 20 mg/kg/day. The sponsor is conducting the study for 9 months to support an IND in humans. CVM stated that a pharmacokinetic study is needed to bridge between the liquid formulation used in this study and the final market formulation.

The sponsor stated that the final market formulation will have four tablet sizes, 25, 50, 100, and 150 mg. CVM requested that the sponsor look at the dose range based upon body weight administered in the safety studies and discuss how this reflects upon safety for the field study. The smallest dogs may be receiving the largest dose per weight.

The sponsor provided a statistical justification for the number of animals used in the field study. CVM stated that while we look for statistical significance, it is important to have a sufficient number of cases to provide adequate inferential value about the use of the drug under actual conditions of use in the target population. It will be the first time the drug is used in dogs with mast cell tumors under the direction of multiple investigators. We also obtain additional information regarding the safety of the drug used in various breeds under actual conditions of use, with the owners dosing the dogs. To obtain this additional information, we ask that a minimum of 100 dogs be treated with the drug. The potential for drop outs and early withdrawals should be taken into consideration when determining



the number of animals to be enrolled in the study. The protocol should address the minimum and maximum number of animals enrolled at each site.

CVM stated that the safety data does not need to be submitted prior to conducting the field study. When the target animal safety is submitted, all raw data for the studies intended to support the technical section should be submitted along with any translations, if needed. Summaries of all other safety studies conducted in any species (e.g., human, rat or dog) should be submitted in the data package.

**Minor Use in a Major Species:**

The minor use guidance was discussed. The drug may qualify as a minor use in a major species. Currently, the guidance provides very little additional benefit. However, there is a new law before Congress. If the law passes, it could provide immediate benefits to the sponsor. Currently there is not a definition to determine what would qualify as a minor use in a major species. The sponsor could provide a proposal with scientific justification stating why the drug should be considered a minor use in the major species.

**Expedited Review Status:**

CVM stated that the drug would probably qualify for expedited review status (ERS). Expedited review status would reduce the review time for each submission and move it up higher in the reviewer's queue. Data submissions normally have a review time of 180 days. ERS reduces the review time to 90 days. The sponsor should submit a request for ERS with a scientific justification to support the request. Please see CVM's Policy and Procedure Manual Guide 1243.3120 on our website for additional information.

**Pharmacokinetic Data:**

The sponsor indicated that several pharmacokinetic studies were conducted, including a radiolabel study providing information on the mass balance and tissue distribution of this drug in dogs. They also noted that a bridging study has already begun comparing the oral solution used in the toxicology/target animal safety study versus the proposed final market formulation. That study employs a laboratory batch of the product at a strength their original write-up suggested would not be manufactured for marketing purposes. CVM indicated that executed bridging study employing a laboratory batch of the proposed product would not be acceptable.

Regarding their inquiry as to whether or not in vitro dissolution data can be used in lieu of submitting any in vivo bioequivalence study data, CVM indicated that this option would not be acceptable. Firstly, this product is poorly soluble (based upon traditional Biopharmaceutics Classification System specifications). Accordingly, this drug would be classified as either Class II (highly permeable, poorly soluble) or Class IV (poorly soluble, poorly permeable). If it is a Class II compound, in vitro/in vivo correlations need to be established before in vitro dissolution data can support in vivo bioequivalence. If it is a Class IV compound, this is considered a highly problematic drug and only in vivo bioequivalence studies would suffice. However, they were informed that when conducting the in vivo bridging (bioequivalence) study, in vitro dissolution data will be needed to support the waiver of the need to conduct studies on the other dosage strengths.

The dissolution method should be consistent with that agreed upon by the Division of Manufacturing Technologies (HFV-140).

The sponsor asked if the largest size tablet needs to be used in the in vivo bioequivalence trial. CVM explained that since veterinary medicine doses on a mg/kg basis, such a requirement would necessitate the use of giant breed animals. Such a requirement is not tenable under most study conditions, and therefore CVM asks only that the highest mg/kg dose is administered to medium size animals. In vivo bioequivalence study requirements for the additional tablet strengths are then waived if there is compositional proportionality to the strength tablets that underwent in vivo bioequivalence evaluation and if acceptable in vitro dissolution data are submitted. CVM also told the sponsor that all pivotal pharmacokinetic studies should be conducted with pilot batches (10% of full production scale batches), not laboratory batches. Accordingly, the pivotal bridging study should be conducted using the pilot batch that will undergo stability testing for the Chemistry, Manufacturing and Controls (CMC) portion of this application.

The sponsor was advised to submit a bridging study protocol, along with the proposed dissolution method and method of analysis (which we assume will be the f2 criterion). Since the bridging study is intended solely to cover safety, we are concerned with only the upper bound, not the lower bound. The lower bound pertains to effectiveness, which will be determined on the basis of clinical trials.

One concern expressed by CVM is the potential for food to increase the extent of drug absorption. The sponsor indicated that since the oral solution is ~85% bioavailable, they don't believe that this will be a problem. Nevertheless, the sponsor needs to provide information confirming that unexpectedly high drug concentrations will not occur if the product is administered in the prandial state. If they have data confirming that the drug is nearly 100% bioavailable as the oral solution under fasted condition, this should be provided to CVM to address this issue. In this regard, it should be noted that AB Science stated that rats tended to have more bone marrow effects than did dogs, and that they believe this to be attributable to the higher serum drug concentrations observed in rats.

A final point of concern pertained to dose bands and the exact dosages used in the safety study. The sponsor noted that the product will be coated to minimize owner exposure to the drug. CVM noted that this, by definition, prevents that the tablets be scored. The sponsor agreed to this point. With this in mind, the proposed tablet strengths will result in a wide range of mg/kg doses, depending upon the weight of the dog. AB Science indicated that they are considering the manufacture of an additional (25 mg) dosage strength. CVM recommended that AB Science provide information on the maximum dose within each of the tablet strengths (based upon weight ranges) and that this will be used to determine the adequacy of doses used in the toxicology/target animal safety study.

**CMC:**

Liver powder is added to the inside of the tablet in case a dog bites the tablet they will not be adverse to taking the pill again. The liver powder is not intended for advertising for palatability. The pills will be coated to protect the owners and won't be scored. The liver flavor is inside the pill, not in the coating.

**Phased Review of the INAD:**

Under the INAD, CVM provides for phased review of the technical sections necessary for approval of a new animal drug. The technical sections are:

- Effectiveness
- Target Animal Safety
- CMC
- Environmental Assessment
- Labeling
- Freedom of Information (FOI) Summary
- All Other Information

Each technical section is submitted separately for review. All data to support the technical section is submitted together. The wording for the labeling relevant to the technical section, as well as the component of the FOI Summary are submitted with each technical section. After all technical sections are complete, an Administrative NADA is filed to request approval.

A client information sheet may be included with the labeling. Various formats are acceptable including a question and answer format.

**U.S. Agent:**

Prior to submitting the Administrative NADA, the sponsor should identify a US Agent. All correspondence regarding the NADA will be directed to them. In the meantime, Anne-Virgine Eggimann and Emmanuelle Voisin are the company contacts for correspondence.

Lisa M. Troutman, MS, DVM  
Veterinary Medical Officer, HFV-112

cc: HFV199/INAD 11206 A0000  
LTroutman/HFV112/12-18-03  
Final: gsg/3-10-04  
cc: CVM Records\ONADE\I011206A0000met.min

# EXHIBIT I

## NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION

**PAPERWORK REDUCTION ACT STATEMENT:** A Federal agency may not conduct or sponsor, and a person is not required to respond to, a collection of information, unless it displays a current valid OMB control Number. The public reporting burden for the collection of information is estimated to vary from 15 minutes to 2 hours, with an average of 30 minutes per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary information, and completing and reviewing the collection of information. Send comments regarding the burden estimate or any other aspect of this collection of information to the Food and Drug Administration, Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

**Submit this notice to:**

Food and Drug Administration  
Center for Veterinary Medicine  
Document Control Unit, HFV-199, Room N-403  
(Attention: Review Division HFV- )  
7500 Standish Place  
Rockville, Maryland 20855

DATE: Feb 1<sup>st</sup>, 2005

INAD / IFA NO: INAD 11206

STUDY / TRIAL ID: AB1010 PIIMCT 04003

DRUG SHIPMENT NO: 1

TYPE OF SHIPMENT:

☒ Initial

☐ Discontinued

☐ Supplement

☐ Other

The sponsor, AB Science 3 Avenue George V, 75008 Paris, France, submits a notice of claimed investigational exemption for the shipment or delivery of a new animal drug under the provisions of 21 CFR 511.1. This information is submitted in paper (in triplicate).

### I. Shipment ☒ or Receipt ☐ Information

1. NAME(S) OF THE DRUG(S)

Established name(s): AB 1010

Trade name(s):

2. PROPOSED USE OF THE DRUG(S): MAST CELL TUMOR TREATMENT

3. DATE OF DRUG SHIPMENT (OR RECEIPT): FEB 03, 2005

4. TOTAL QUANTITY (WT. OR VOL.) AND CONCENTRATION OF DRUG(S) SHIPPED (OR RECEIVED): 32 BOTTLES OF 50 TABLETS

Each tablet contains 25, 100 or 150 mg AB1010base or is the matching placebo

5. TYPE OF STUDY / TRIAL: DOUBLE-BLIND RANDOMIZED STUDY VS PLACEBO

6. INTENDED USE OF STUDY OR TRIAL:

☒ Pivotal (intended for support of NADA or ANADA)

☐ Non-pivotal

7. NAME AND ADDRESS OF INVESTIGATOR: DAVID ARGYLE

UNIVERSITY OF WISCONSIN, SCHOOL OF VETERINARY MEDICINE

2015 LINDEN DRIVE

MADISON WI 53703-1102

Phone Number: 608-262-5990

8. LOCATION OF STUDY / TRIAL: UNIVERSITY OF WISCONSIN, SCHOOL OF VETERINARY MEDICINE

2015 LINDEN DRIVE

MADISON WI 53703-1102

9. NAME AND ADDRESS OF STUDY MONITOR: DIANE PROBASCO

Phone Number:

10. APPROXIMATE DATE OF STUDY / TRIAL Start: February 2005 Finish: DECEMBER 2005

11. PROTOCOL SUBMITTED TO CVM:

☒ Yes

☐ No

If Yes, date submitted to CVM and/or CVM submission number: FEB 10, 2005

12. SPECIES OF ANIMALS: DOG

13. SIZE AND TYPE OF ANIMALS: ANY

14. APPROXIMATE NUMBER OF ANIMALS IN THIS STUDY/TRIAL:

Total: 125

Treated: 100

Control: 25

15. NUMBER OF ANIMALS PREVIOUSLY USED:

Total: 0

Treated:

Control:

16. MAXIMUM DAILY DOSE: 12.5 MG/KG

AND DURATION: 6 MONTHS

17. METHOD OF ADMINISTRATION: ORAL ROUTE

18. CONTRACT RESEARCH ORGANIZATIONS (CRO) USED:

☒ Yes

☐ No

Name and address of CRO: Harrison Clinical Research

Phone Number:

Description of obligations transferred to CRO: study monitoring

## II. Animals Intended For Human Food Purposes

1. DATE OF CVM AUTHORIZATION LETTER:

2. WITHDRAWAL PERIOD:

3. ACKNOWLEDGEMENT: Acknowledgment that the date and place of slaughter will be reported to FDA and Dr. Julie Cornett, USDA/FSIS, Technical Service Center, 1299 Farnam Street, Suite 300, Landmark Center, Omaha, NE, 68102, at least 10 days prior to shipment for slaughter. Experimentally treated animals will be identified to the inspector in charge of the slaughtering establishment when presented for antemortem inspection.

☐ Yes

☐ No

4. NOTIFICATION WAIVER: A waiver of requirements for notification of the date and place of slaughter after a 30-day holding and observation period following the required withdrawal period has been granted by FDA.

☐ Yes

☐ No

## III. Investigational New Animal Drug Labeling (Please select one label)

1. NEW ANIMAL DRUGS FOR TESTS *IN VITRO* AND IN LABORATORY RESEARCH ANIMALS:

☐ **Caution.** Contains a new animal drug for investigational use only in laboratory research animals or for tests *in vitro*. Not for use in humans.

2. NEW ANIMAL DRUGS FOR CLINICAL INVESTIGATION IN ANIMALS:

☒ **Caution.** Contains a new animal drug for use only in investigational animals in clinical trials. Not for use in humans. Edible products of investigational animals are not to be used for food unless authorization has been granted by the U.S. Food and Drug Administration or by the U.S. Department of Agriculture.

3. NEW ANIMAL DRUGS FOR EXPORT IN ANIMALS:

☐ **Caution.** Contains a new animal drug for use only in investigational clinical trials. Not for use in humans. Edible products from animals used for investigation are not to be used for food in any manner contrary to the requirements of the country in which the clinical trials are to be conducted.

If the drug is intended for food-producing animals, the label must also bear:

☐ No official withdrawal time has been established for this product under the proposed investigational use.

## IV. Sponsor Information

1. SPONSOR'S NAME: AB SCIENCE

2. SPONSOR'S ADDRESS: 3 AVENUE GEORGE V  
75008 PARIS  
FRANCE

3. SPONSOR CONTACT'S SIGNATURE:

4. SPONSOR CONTACT'S NAME: ALAIN MOUSSY

5. SPONSOR CONTACT'S PHONE NUMBER: +33 147 20 23 11

6. SPONSOR CONTACT'S FAX NUMBER: +33 147 20 24 11

7. SPONSOR CONTACT'S E-MAIL ADDRESS: ALAIN.MOUSSY@AB-SCIENCE.COM

## V. Comments

Are there additional comments?

~~Yes~~

No

INAD/IFA No.:

DATE:

**NOTE:** IF THE INVESTIGATION IS DISCONTINUED, THE CENTER FOR VETERINARY MEDICINE SHOULD BE NOTIFIED, GIVING THE REASON AND DISPOSITION OF THE DRUG.

## EXHIBIT J



PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 7,423,055

Docket No. 71247-0144

Issued: September 9, 2008

To: Ciufolini et al.

For: : 2-(3-AMINOARYL)AMINO-4-  
ARYLTHIAZOLES FOR  
THE TREATMENT OF DISEASES

Assignee: AB Science

APPOINTMENT OF SPECIAL POWER OF ATTORNEY

Commissioner for Patents  
Alexandria, VA 22313-1450

Sir:

AB SCIENCE, the undersigned assignee in the above-captioned patent, hereby appoints Conrad J. Clark (Reg. No. 30,340), and Christopher W. Brody (Reg. No. 33,613) as attorneys with full power to make an application for patent term extension for the above-captioned United States Patent No. 7,423,055 and to transact all business in the Patent and Trademark Office in connection with said application for patent term extension.

Please send all correspondence in connection with the patent term extension to:

Customer No. 22902  
CLARK & BRODY  
1700 Diagonal Road, Suite 510  
Alexandria, VA 22314  
Telephone: 202-835-1111  
Facsimile: 703-504-9415

Respectfully submitted,

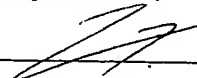
Signature:

Printed Name:

Title:

Date:

Telephone No.

  
\_\_\_\_\_  
Alain Nowssy  
\_\_\_\_\_  
CEO AB Science  
\_\_\_\_\_  
Jan 28<sup>th</sup> 2011  
\_\_\_\_\_  
1  
\_\_\_\_\_